IN THE HON'BLE HIGH COURT OF DELHI

AT NEW DELHI

WRIT PETITION (CIVIL) NO. __ OF 2026

IN THE MATTER OF A PUBLIC INTEREST LITIGATION

IN THE MATTER OF:

Dr. Sujata Mittal & Anr. ...Petitioner(s)

Vs.

Union of India and Others ...Respondent(s)

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SYNOPSIS

The Petitioners are constrained to file the present petition to protect the constitutional rights of young girls, especially their right to life, personal liberty, bodily autonomy, and informed consent under Articles 21 and 19 of the Constitution of India.

The petition concerns the decision of the Government of India to include the HPV vaccine, Gardasil, in the Universal Immunization Programme as part of a nationwide vaccination programme for girls aged approximately 14 years. In the implementation of this programme, vaccines are being administered in schools and through public health systems without proper informed consent or prior approval from parents. Reports suggest that frontline health workers, including ASHA workers, are given targets to increase enrolment, which in many cases leads to undue pressure on young girls to take the vaccine. It is submitted that the entire programme has been launched without any credible data with respect to the efficacy of the vaccine and the actual requirement of the population.

It is respectfully submitted that a 14-year-old girl from Tamil Nadu received the HPV vaccine on 30.03.2026 at the Government Hospital, Kanai. Within three to four days she developed serious and worsening symptoms, loss of voice, paralysis-like weakness on one side of the body, inability to walk, and blurred, dim vision. She was admitted to the ICU in a critical condition on oxygen support, catheter, and intravenous medication, and remained bedridden for several days without significant improvement. Similar incidents reported from Gwalior and Bihar raise serious concerns regarding vaccine safety and monitoring.

The Petitioner submits that the entire exercise is in violation of the settled position of law. The jurisprudence of bodily integrity is protected under Article 21 of the Constitution of India, and no individual can be compelled to undergo vaccination. This Hon'ble Court has consistently held that personal autonomy

includes the right of an individual to determine how they live their own life, which consequently encompasses the right to refuse to undergo any medical treatment in the sphere of individual health.

In the past, serious concerns were raised regarding the safety and regulation of the HPV vaccine in India. In 2010, several deaths were reported in connection with Gardasil and Cervarix. The 72nd Parliamentary Standing Committee Report on Health and Family Welfare (2013) examined these concerns and found grave irregularities in the conduct of the clinical trials, including deviations from established protocols and serious lapses in obtaining participant consent.

Despite this initial setback, several States undertook independent initiatives to introduce the HPV vaccine. Delhi became the first State to launch a public HPV vaccination programme for school children. In November 2016, the Government of Punjab initiated a similar campaign in the districts of Bathinda and Mansa, which had relatively high incidence rates of cervical cancer, targeting girls studying in Class 6 in government schools and covering nearly 10,000 beneficiaries across hundreds of schools. Subsequently, in 2018, the State of Sikkim implemented a comprehensive school-based programme targeting approximately 25,000 girls aged 9 to 13 years.

It is submitted that HPV is sexually transmitted, and though types 16 and 18 are linked to cervical cancer, most infections resolve on their own. HPV is only one factor among several, poor hygiene, early marriage, multiple pregnancies, multiple partners, smoking, oral contraceptives, weak immunity, and poor nutrition, none of which vaccination addresses. The burden must also be seen in context, Mortality is about 0.01% of the population, and both incidence and mortality have declined steadily without any vaccination programme, as National Cancer Registry Programme data between 1982 and 2005 reflects.

Further, studies on HPV vaccines have limitations. An independent analysis of multiple clinical trials has found that these studies were not designed to

directly show that the vaccine prevents cervical cancer, but instead relied on indirect indicators. Therefore, the long-term effectiveness of the vaccine remains uncertain. On the other hand, medical experts agree that regular screening of women between the ages of 30 and 65 years is the most effective way to prevent cervical cancer. The present programme, however, focuses mainly on vaccinating young girls, and aims to vaccinate approximately 1.15 crore girls aged 14 years, who are at a relatively lower immediate risk.

It is respectfully submitted that significant safety concerns regarding the Gardasil HPV vaccine have emerged internationally, with Merck & Co. announcing on 04 June 2026 a settlement exceeding USD 50 million in more than 200 lawsuits alleging serious autoimmune, cardiovascular, and reproductive disorders following vaccination. The litigation formed part of the consolidated federal proceedings titled *In re: Gardasil Products Liability Litigation (MDL No. 3036)* and related state court proceedings in California. The dismissal of the lead trial shortly before Merck's settlement announcement prevented judicial scrutiny of the safety evidence through a jury verdict. Merck's February 2026 Annual Report further disclosed that a settlement framework had been reached in October 2025, and that the settlement was considered less costly than continuing to defend the litigation.

In these circumstances, the Petitioner submits that the current rollout of the HPV vaccination programme raises serious concerns regarding consent, safety, scientific basis, and public health priorities, and therefore requires consideration by this Hon'ble Court.

List of Dates

2009	The ICMR in collaboration with PATH (Program for Appropriate Technology in Health) launched the administration of the clinical trials of the HPV vaccine in the state of Gujarat and Andhra Pradesh.

2010	Several deaths were reported in Khammam District of Andhra Pradesh due to the clinical trials.
2013	The 72nd Parliamentary Standing Committee Report on Health and Family Welfare (2013), found grave irregularities in the conduct of clinical trials, highlighted deviations from established protocols and serious lapses in obtaining proper consent from trial participants.
2021	MSD Pharmaceuticals Pvt Ltd a wholly owned subsidiary of Merck launched India's first Gender Neutral HPV Vaccine.
2022	GSK discontinues ceravix in India due to low demand in India.
2022	The National Technical Advisory Group of Immunization (NTAGI) recommended the introduction of the HPV Vaccines in India as a part of the Universal Immunization Programme (UIP).
July 2022	The Drug Controller General of India (DGCI) granted the market authorization to the Serum Institute to develop the first indigenously developed Quadrivalent Human Papillomavirus Vaccine (qHPV) for Cervical Cancer known as CERVAVAC.
28.02.2026	The union Ministry of health and family welfare, formally launched the vaccine under the UIP.

11.03.2026	It was reported in various newspapers that few girls were hospitalized due to adverse effects of the vaccines in Gwalior, Madhya Pradesh.
30.03.2026	A 14-year-old girl from Kanaiyakkupam Village, Villupuram, received the HPV vaccine on 30.03.2026 at Kanai Government Hospital. Within three to four days, she developed serious symptoms including loss of voice, one-sided weakness resembling paralysis, inability to walk, and blurred vision.
16.04.2026	Three girls fainted and were hospitalised in Begusarai Bihar after taking the HPV Vaccine.
27.04.2026	Petitioner No. 1, addressed formal representations to all the Respondents. The said representations did not elicit any satisfactory response.
07.05.26	Respondent No. 3 sent a vague and unconvincing reply via email, failing to address the grievances raised.
04.06.26	Merck & Co., Inc. publicly announces settlement of more than 200 lawsuits filed in the United States of America alleging that the Gardasil vaccine caused serious autoimmune ailments in young women, for a sum exceeding USD 50 million, without admission of liability.
.07.2026	Hence this petition

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A Public Interest Litigation under Article 226 of the Constitution of India seeking issuance of writ of Mandamus or any other appropriate writ against the respondents for violation of fundamental rights under Article 21 read with Article 19 of the Constitution of the young girls more particularly addressing the issue of violation of their personal liberty, informed consent and bodily autonomy.

TO,

THE HON'BLE CHIEF JUSTICE

AND HIS COMPANION HON'BLE JUSTICES OF

THE HON'BLE HIGH COURT OF DELHI

THE HUMBLE PETITION OF THE

PETITIONER ABOVE NAMED

MOST RESPECTFULLY SHOWETH:

1. The present Writ Petition is filed in public interest under Article 226 of the Constitution of India, invoking the extraordinary jurisdiction of this Hon'ble Court for the enforcement of fundamental rights guaranteed under Part III of the Constitution. The issues raised in the present petition concern the protection of the right to life and personal liberty under Article 21, the right to equality under Article 14, and the right to freedom of speech and expression under Article 19(1)(a), particularly in the informed consent in public health interventions. The present petition seeks urgent judicial intervention in relation to the national rollout of the HPV vaccine, raising significant concerns impacting girls age 14 year old and prays for the issuance of appropriate directions to ensure transparency, accountability, and safeguarding of fundamental rights. The petitioners submits that they do not have personal interest in the litigation and that the petition is not guided by the self gain of any other person/institution/body and that there is no motive other than of the public interest in filing the writ petition.

2. The petitioners submits that the present petition is based on the source of knowledge of the facts alleged in the writ petition are drawn from authentic scientific journals and other relevant documents and the further inquiries/investigation made to determine the veracity of the same.

7. The petitioners submits that no other public interest litigation or any other Petition on the present subject matter has been filed before any other court including this Court by the petitioners.
8. The Respondent no. 1 is a Union of India through the Ministry of Health and Family welfare, a nodal agency in India responsible for the enforcement of the right to health of the citizens of India.
9. The Respondent no. 2 is Indian Council of Medical Research is the apex body in India for the formulation, coordination and promotion of biomedical research, and spearheads innovation through a wide range of initiatives and collaborations. ICMR also contributes to the formulation of evidence-based health policies and programs through its guidelines, regulations and policy inputs.
10. Respondent no. 3 is India's national regulatory authority responsible for approving new drugs, regulating clinical trials, and ensuring drug safety. It is tasked with safeguarding public health by mandating rigorous scientific evaluation before approving pharmaceutical products.
11. Respondent no. 4 National Technical Advisory Group on Immunization (NTAGI) is the main expert body in India that advises the government on vaccines and immunisation policy.
12. It is respectfully submitted that the present petition is being filed in the larger public interest, with the objective of addressing issues that have a

direct bearing on public health, safety, and regulatory accountability. The Petitioners do not have any personal, private, or pecuniary interest in the subject matter of the present petition. The petition is not motivated by any individual gain, oblique purpose, or extraneous consideration, but is instituted solely to secure the protection of fundamental rights and to ensure that appropriate safeguards are in place in matters affecting the general public.

13. The Petitioners respectfully submit that this is their first Public Interest Litigation. They further affirm that they have not filed any other Public Interest Litigation or submitted any letter petition on the present subject matter before this Hon'ble Court or before any other court. The present petition is therefore filed independently and in good faith.

14. It is respectfully submitted that there is no efficacious alternative remedy available to the Petitioners, and therefore the present petition has been filed by invoking the jurisdiction of this Hon'ble High Court.

15. The Petitioners further submits that the requisite court fee has been duly affixed and the petition has been filed within the prescribed period of limitation. It is also submitted that the present petition has been filed bona fide, and it is expedient in the interest of justice that the reliefs sought herein be granted.

Cause of Action

16. Human Papillomavirus (HPV) is a sexually transmitted virus. Of the 200 HPV types identified, most infections are asymptomatic and resolve spontaneously. The prevalence of HPV infection across countries ranges from 2% to 42%. Type 16 HPV is considered to pose the highest risk of cervical cancer, followed by Type 18. Subtypes 16 and 18 together account for approximately 70% of cases of invasive cervical cancer. Subtypes 6 and 11 lead to genital warts but not cancer.

17. HPV has been identified as a necessary but not sufficient cause of cervical cancer. Cervical cancer is additionally associated with poor genital hygiene, early age of marriage, repeated pregnancies, multiple sexual partners, prolonged use of oral contraceptive pills, smoking, immunosuppression, and nutritional deficiencies. These cofactors operate regardless of HPV type and are not addressed by vaccination.

18. The mortality rate from cervical cancer in India is approximately 0.01% of the population. Critically, cervical cancer incidence and mortality has been declining steadily in India without any vaccination programme. The National Cancer Registry Programme (NCRP) report on Time Trends in Cancer Incidence Rates 1982 - 2005 records a statistically significant decline in age-adjusted cervical cancer incidence in urban registries from 42.3 per 100,000 in 1982 - 83 to 22.3 per 100,000 in 2004–05, a decline of 32% without any vaccination. A true copy is annexed as **Annexure P/2 at page no** 55 to 237

19. Therefore the case of the petitioner before Hon'ble Court is as follows

a. The introduction of the Human Papillomavirus (HPV) vaccine in India has developed over time through early pilot projects.The first phase started in July and August 2009, when the Program for Appropriate Technology in Health (PATH), a non-governmental organisation based in Seattle, carried out HPV vaccination projects in Andhra Pradesh and Gujarat. These projects were conducted in partnership with the Indian Council of Medical Research (ICMR) and the respective state governments. The programme targeted girls between the ages of 10 and 14 years and used two vaccines Gardasil, manufactured by Merck, and Cervarix, produced by GlaxoSmithKline. Around 23,000 to 42,000 girls were covered.

b. Soon after, the project became controversial. Reports were published about the deaths of some girls who had received the vaccine, with the number later stated as seven. This incident led to public concern and scrutiny. Further inquiries, including findings released in 2013, identified serious issues highlighting how the project was conducted. These included problems with informed consent, where in some cases consent forms were signed by hostel wardens instead of parents or legal guardians, and the inclusion of girls from vulnerable and marginalised groups.

c. The issue was also examined by a Parliamentary Standing Committee. The Committee raised concerns about possible conflicts of interest involving non-government entities, and ICMR. It questioned whether financial and institutional links between these bodies affected how the project was designed and carried out, and whether this had an impact on the welfare of participants. This episode influenced later policy decisions and contributed to caution in introducing HPV vaccination more widely. A true copy 72nd Report of the Dept.-Related Parliamentary Standing Committee on Health and Family Welfare - “Alleged Irregularities in the Conduct of Studies Using HPV Vaccine by PATH in India” (August 2013) is marked and annexed as **Annexure P/3 at page no 238 to 280**

d. After this period, some states introduced HPV vaccination programmes on their own. Delhi became the first state to start a public HPV vaccination programme for school children on November 7, 2016, on National Cancer Awareness Day. Later that month, on November 23, 2016, Punjab started a similar programme in the districts of Bathinda and Mansa, where cervical cancer rates were relatively higher. This programme targeted girls in Class 6 in government schools and covered nearly 13,000 girls.

A true copy of the news published in the Print dated 28th January 2022 is marked and annexed as **Annexure P/4 at no 281 to 284**

A true copy of the news published in the Times of India dated 9th November 2017 is marked and annexed as **Annexure P/5 at page no 285 to 286**

e. In 2018, Sikkim introduced an HPV vaccination programme for girls aged 9 to 13 years, mainly through schools. About 25,000 girls were targeted under this programme.

f. In June 2022, the National Technical Advisory Group on Immunisation (NTAGI) recommended that HPV vaccines be included in India's Universal Immunisation Programme (UIP). In July 2022, the Drugs Controller General of India (DCGI) approved Cervavac, a quadrivalent HPV vaccine developed by the Serum Institute of India. This approval was an important step towards increasing domestic supply. A true copy of the information bulletin published by the Press Information Bureau dated 22 DEC 2022 is marked as **Annexure P/6 at page no 287**

g. In 2023, NTAGI suggested a phased approach for introducing the HPV vaccine. It recommended a one-time catch-up campaign for girls aged 9 to 14 years, followed by routine vaccination at 9 years of age. However, plans to include the vaccine in the UIP during 2023–2024 were delayed due to logistical, financial, and policy issues.

h. The delay between 2023 and early 2026 was due to several reasons. Imported vaccines such as Gardasil were expensive and not easily available in large quantities. Domestic production of Cervavac was still increasing and could not meet large-scale demand at that time. There were also budget limitations. Concerns from the earlier 2009–2010 controversy continued to affect decision-making. In addition, further studies were needed to confirm whether Cervavac could be used as a single-dose vaccine, with results expected around 2027. Other challenges included low awareness, social concerns about vaccinating young girls for a sexually transmitted infection, and the need for systems to monitor adverse events.

i. Finally a nationwide HPV vaccination campaign launched on February 28, 2026. The campaign targeted about 1.15 crore girls who had completed 14 years but were not yet 15. It used a single dose of the Gardasil-4 vaccine, in line with recommendations from the World Health Organization. The vaccine was provided free of cost at government health facilities such as Primary Health Centres, Community Health Centres, District Hospitals, and Medical Colleges.

j. The campaign was carried out through schools and community outreach programmes. Vaccination data was recorded using the U-WIN digital platform. The campaign was planned for 90 days and

is expected to be followed by inclusion in the routine UIP. Consent from parents or guardians was made mandatory.

k. It is very important to note that, as of early 2026, Cervavac has not yet been included in the routine Universal Immunisation Programme. This is mainly because studies are still ongoing to confirm its use as a single-dose vaccine, and it is also awaiting World Health Organization prequalification. There are also some remaining policy concerns. It is expected that Cervavac may be used more widely in the future once these issues are resolved.

l. It is respectfully submitted that a 14-year-old girl from Kanaiyakkupam Village, Villupuram, received the HPV vaccine on 30.03.2026 at Kanai Government Hospital. Within three to four days, she developed serious symptoms including loss of voice, one-sided weakness resembling paralysis, inability to walk, and blurred vision. She is currently in critical condition in the ICU, on oxygen and IV support, and has remained bedridden without improvement. This incident has been reported by local news channel Polimer News https://www.youtube.com/watch?v=AARiU9IlIAs accessed on 18th April 2026

m. It is important to note various newspapers reported that few girls were hospitalized due to adverse effects of the vaccines in Gwalior, Madhya Pradesh. Three girls fainted and were hospitalized in

Begusarai Bihar after taking the HPV Vaccine. A true copy of the news published in Free Press Journal dated 11.03.2026 along with other news reports are marked and annexed as **Annexure P/7 at page no** 288 to 292

20. The petitioner submitted that before such a mass vaccination program approved, the Government must commission or disclose a robust, district-level epidemiological assessment, peer-reviewed and publicly available so that citizens, health professionals, and independent experts may evaluate whether the proposed intervention is proportionate and consistent with the actual burden of disease. However, no such assessment has been publicly disclosed.

Efficacy of the Vaccine

21. The study by Anna-Barbara Moscicki and her co-authors, published in JAMA in 2004, examined how cervical abnormalities behave in young women. It found that low-grade lesions (CIN 1) often go away on their own without any treatment. A large number of cases showed natural healing within a few years. The study suggests that in many young women, these early abnormalities are temporary and the body is able to clear them naturally. A true copy of the Moscicki AB, Shiboski S, Hills NK, et al. *Regression of low-grade squamous intra-epithelial lesions in young women.* Published in JAMA, 2004; 292(23): 2999–3006 is marked and annexed as **Annexure P/8 at page no** 293 to 298

22. The meta-analysis by Jeanne Melnikow and her team, published in Obstetrics & Gynecology in 1998, combined results from many different studies to understand what usually happens to cervical lesions over time. It found that about 60% of mild lesions (CIN 1) and around 40% of moderate lesions (CIN 2) regress without treatment. This study is widely used to show that a significant number of such lesions resolve naturally, which is why careful monitoring is sometimes preferred over immediate intervention.A true copy of the study conducted by Melnikow J, Nuovo J, Willan AR, Chan BK, Howell LP.*Natural history of cervical squamous intraepithelial lesions: a meta-analysis.* Published in Obstetrics & Gynecology, 1998; 92(4 Pt 2): 727–735 is marked and annexed as **Annexure P/9 at page no** 299 to 307

23. The work associated with Maria Kyrgiou, including studies published in journals like BMJ, examined the outcomes related to cervical lesions and their treatment. While much of this research focuses on the effects of medical procedures, it also supports the broader understanding that not all cervical lesions progress to cancer and that some may regress over time. These studies contribute to the overall evidence base used in assessing how such conditions should be managed. A true copy of the Kyrgiou M, Koliopoulos G, Martin-Hirsch P, et al. *Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early*

invasive disease. Published in BMJ, 2006 is marked and annexed as **Annexure P/10 at page no** 308 to 317

24. An independent analysis of 12 published Phase 2 and 3 randomised controlled efficacy trials of HPV vaccines Cervarix and Gardasil, published in the Journal of the Royal Society of Medicine (Rees, Brhlikova & Pollock, 2020), concluded that the trials were not designed to detect cervical cancer. *A true study conducted by Rees CP, Brhlikova P, Pollock AM. Will HPV vaccination prevent cervical cancer? J R Soc Med. 2020 Feb;113(2):64-78. doi: 10.1177/0141076819899308. Epub 2020 Jan 21. PMID: 31962050; PMCID: PMC7068772* **Annexure P/11 at page no** 318 to 332

25. It is submitted that in India there is a lack of conclusive data regarding the duration of immunological protection provided by the vaccine. Existing studies have followed vaccinated individuals for only about 5 to 15 years. However, those vaccinated between the ages of 9 and 14 will reach the peak risk age for cervical cancer in India, estimated at 55 to 59 years, only after 40 to 50 years. In such circumstances, the duration and effectiveness of vaccine protection over this long period remain uncertain and unproven.

C. Prior Regulatory Violations and Reported Mortalities

26. An HPV vaccine demonstration project run by PATH in Gujarat and Andhra Pradesh involved more than 23,000 girls. This project was suspended by the Government of India in April 2010 after reports of

deaths of four girls and alleged ethical violations. The DG ICMR admitted to the Parliamentary Standing Committee on April 29, 2010 that 'DCGI's guidelines had not been adhered to' in the clinical trial.

27. The 72nd Report of the Parliamentary Standing Committee on Health and Family Welfare found that the project 'had breached medical ethics and violated Indian regulations on clinical trials.' The Committee raised grave concerns about the overlapping financial interests of non-governmental organizations with ICMR, and recommended legal action against PATH for 'violation of human rights and clinical trial rules.'

28. Its submitted that a civil-society field report from a visit to Bhadrachalam (the Bhadrachalam Field Report) recorded that parents 'were not even informed' that their daughters were being vaccinated, that girls reported 'their parents were not informed and their signatures were not taken,' and that in one hostel 'the teacher in charge had given consent for vaccination of around 300 girls', a substitution of parental consent with institutional consent that is unlawful. The same report records that 'two of the deaths have been written off as suicides when the parents clearly state that they were not,' and that 'no follow-up treatment has been provided for girls who have been facing side effects.' A true copy of this report is annexed as **Annexure P/12 at page no** 333 to 357

29. Despite this documented history of regulatory violations, ethical breaches, contested deaths, and parliamentary censure, the Government

proceeded to include the HPV vaccine in the UIP without publicly addressing or resolving any of these prior concerns.

D. The National Rollout - NTAGI, DCGI, and the Scale of the Programme

30. In June 2022, the National Technical Advisory Group on Immunisation (NTAGI) recommended the introduction of HPV vaccines in India's Universal Immunisation Programme (UIP), with a one-time catch-up campaign for girls aged 9-14 followed by routine introduction. A True copy of Lok Sabha Unstarred Question No. 800 answered on 7th February, 2025 by the Minister of State in the Ministry of Health and Family Welfare - Mr Pratap Rao Jadhav is marked and annexed as **Annexure P/13 at page no** 358 to 359

31. In July 2022, the Drugs Controller General of India (DCGI) granted market authorisation to the Serum Institute of India (SII) for India's first indigenously developed Quadrivalent HPV vaccine, known as CERVAVAC. The Ministry wrote to seven state governments in January 2023 to begin rollout preparations. Operational preparations contemplated vaccinating 68 million girls, primarily through schools, using the U-WIN digital platform for registration and reporting. A true copy of the news published in the MINT 12th July 2022 is marked and annexed as **Annexure P/14 at page no** 360 to 362

32. The decision to proceed with school-based mass vaccination of 1.2 Cr Girls that makes it as one of the largest HPV vaccination drive of its kind was made without:

a. comprehensive, independent, publicly available epidemiological justification;

b. resolution of the prior ethical and regulatory violations documented by Parliament;

c. an independent adverse event surveillance and compensation mechanism; or

d. a mandatory informed consent protocol compliant with established legal standards.

e. Evaluating pre-existing health conditions of the girls in compliance with Govt own guidelines.

A true copy of the news published in by the Times of India dated 25th Feb 2026 is marked and annexed as **Annexure P/15 at page no 363 to 364**

E. Conflicts of Interest in the Approval Process

33. The integrity of the recommendation and approval process has been compromised by undisclosed or inadequately managed conflicts of interest. The 72nd Parliamentary report categorically held that

a. That there was serious dereliction of duty by many of the Institutions and individuals involved. The Committee observes that

ICMR representatives, instead of ensuring highest levels of ethical standards in research studies, apparently acted at the behest of the PATH in promoting the interests of manufacturers of the HPV Vaccine.

b. The committee suggested that it is unwise on the part of ICM R to go in the PPP mode with PATH, as such an involvement gives rise to grave Conflict of Interest. The Committee takes a serious view of the role of ICMR in the entire episode and is constrained to observe that ICMR should have been more responsible in the matter. The Committee strongly recommends that the Ministry may review the activities of ICMR functionaries involved in the PATH project.

34. Thus, petitioners believe that the recent approval process of the HPV vaccination program was compromised and in the manner it has been implemented raises serious concern regarding involvement of private entities in an important public function.

F. Safety - Adverse Events and the Absence of a Compensation Mechanism

35. The Petitioner submits that, in its present form, India lacks an effective and reliable mechanism for reporting adverse events arising from vaccines. Although institutional frameworks such as the Pharmacovigilance Programme of India and the Adverse Events Following Immunization (AEFI) system exist, they do not function as comprehensive, accessible, and mandatory reporting mechanisms in practice. Reporting remains

passive, with no robust system ensuring real-time data collection, independent verification, and transparent public disclosure. Consequently, adverse events and potential side effects often go unreported or uninvestigated, thereby undermining post-vaccination safety surveillance and depriving both regulators and the public of critical information necessary for informed decision-making.

36. In such a scenario, the rollout of a mass vaccination programme involving a vaccine that does not demonstrate clear and significant therapeutic efficacy poses a serious risk to the public healthcare system. Administering a medical intervention at scale without reliable evidence of meaningful benefit, particularly in the absence of a robust adverse event reporting and monitoring framework, may lead to avoidable health risks, misallocation of limited public resources, and erosion of public trust in immunisation programmes. It also undermines the foundational principles of evidence-based public health policy, which require that large-scale interventions be supported by demonstrable safety, efficacy, and continuous post-market surveillance.

G. Global Evidence of Adverse Events - Settlement of Gardasil Litigation in the United States of America

37. It is respectfully submitted that the safety concerns in respect of the Gardasil HPV vaccine have been judicially and commercially acknowledged in the United States of America as well, where on 4th June 2026, Merck &

Co., Inc., the manufacturer of the Gardasil vaccine that has been introduced into India's Universal Immunisation Programme, publicly announced the settlement of more than 200 lawsuits alleging that the said vaccine caused serious autoimmune ailments in young women including Postural Orthostatic Tachycardia Syndrome, Premature Ovarian Insufficiency, Complex Regional Pain Syndrome, and other conditions adversely affecting the cardiovascular and reproductive systems, for a sum exceeding USD 50 million.

38. It is submitted that these lawsuits were consolidated at the federal level as *In re: Gardasil Products Liability Litigation*, MDL No. 3036, before the United States District Court for the Western District of North Carolina, and at the state level as *Jennifer Robi v. Merck & Co.*, Case No. BC628589, before the Superior Court of California, County of Los Angeles, wherein the plaintiff, permanently confined to a wheelchair at the age of 16 years following administration of the Gardasil vaccine, had filed the first Gardasil case to be set for jury trial, which was subsequently dismissed with prejudice on 2nd June 2026, simultaneously with Merck's public announcement of the broader settlement, thereby depriving the public of any jury verdict upon the safety evidence pertaining to the said vaccine.

39. It is further submitted that Merck's own Annual Report of February 2026 discloses that a proposed settlement agreement had been reached as early as October 2025, and that the settlement amount was stated by the

manufacturer to be "considerably less than Merck's anticipated costs" of defending the said litigation, which admission demonstrates that the manufacturer found it commercially rational to pay in excess of USD 50 million rather than submit adverse event data to jury scrutiny. A true copy of the news published in the Claims Journal dated 5th June 2026 is marked and annexed as **Annexure P/16 at page no** 365 to 366

H. Informed Consent - Legal Standard and Current Failures

40. The Delhi High Court, in Master Haridaan Kumar v. Union of India (2019), directed that all government vaccination campaign advertisements must clearly include the risks, side effects, and contraindications of the vaccine. A true copy of this judgement is annexed as **Annexure P/17 at page no** 367 to 372

41. The right to informed consent requires that prior to vaccination, parents and recipients must be provided with complete, accurate, and honest information about: (i) the ingredients of the vaccine including active and inactive components; (ii) the adverse event profile including serious and rare events; (iii) the surrogate endpoint basis of approval (CIN, not cancer); (iv) the absence of long-term efficacy data; and (v) the right to refuse without consequences. The current HPV vaccine rollout does not comply with this standard. Parents cannot be compelled to consent, and no one may ask them to justify their refusal.

I. The Screening Alternative - What Is Being Displaced

42. Fewer than 5% of eligible women in India have ever been screened for cervical cancer. Government-sponsored population-based screening programmes are almost non-existent. The most cost-effective intervention for cervical cancer in the Indian context is early detection through organised screening programmes combined with accessible treatment, not mass vaccination of children for a disease that will take 40 - 50 years to manifest, using a vaccine with an incompletely characterised safety profile and unproven long-term efficacy.

43. In contrast, an example for the United States provides that only marginal improvement in cervical cancer risk reduction compared to screening alone, treatment of women with confirmed cervical cancer diagnoses would cost the public healthcare system considerably less than mass vaccination. Policy-oriented sources explicitly recommend integrating HPV vaccination with strengthened screening, a dual approach rather than vaccine-only scaling. The current programme displaces investment in screening infrastructure with a vaccine-only strategy. *A true copy of the study Kim JJ, Goldie SJ. Health and Economic Implications of HPV Vaccination in the United States. New England Journal of Medicine. 2008;359:821–832 marked and annexed as* **Annexure P/18 at page no 373 to 389**

J. No Fault Compensation regime

44. It is respectfully submitted that India presently does not have a uniform or structured no-fault compensation mechanism to provide redress to persons who suffer serious adverse events following vaccination. In *Rachana Gangu v. Union of India*, (2026 INSC 218) the Supreme Court took note of this gap and directed the Union of India, through the Ministry of Health and Family Welfare, to frame a no-fault compensation policy for serious adverse events following COVID-19 vaccination. The underlying principle of the said decision should not be confined only to the COVID-19 vaccine, but extends to the broader need for a fair and consistent compensation framework for vaccine-related adverse effects. In the absence of such a policy, the process of ascertaining and awarding compensation to affected individuals becomes uncertain and difficult, thereby leaving victims without an effective and timely remedy.

45. In view of the aforesaid points it is submitted that the programme has been introduced in India without placing on record any credible, India-specific data or comprehensive studies demonstrating the long-term efficacy of the vaccine or establishing the actual need of such large-scale administration within the target population. It is submitted that there is an absence of transparent, publicly available material assessing population-specific risk factors, disease burden, cost-benefit considerations, and long-term outcomes in the Indian context. In the absence of such evidence-based evaluation, the indiscriminate rollout of the programme raises serious concerns regarding scientific justification,

proportionality, and the safeguarding of public health, particularly when it involves administration to minors on a mass scale.

Grounds

I. Bodily integrity is protected under Article 21 of the Constitution of India and no individual can be forced to be vaccinated. Personal autonomy of an individual involves the right of an individual to determine how they should live their own life, which consequently encompasses the right to refuse to undergo any medical treatment in the sphere of individual health.

II. It is submitted that the actions of the Respondents are in violation of Article 21 of the Constitution of India. The right to life includes the right to dignity, bodily integrity, and personal autonomy. No individual can be compelled to undergo vaccination, as it constitutes an intrusion into the body. Personal autonomy protects the right of every individual to make decisions regarding their own health, including the right to refuse medical treatment, even where such refusal may have serious consequences.

III. It is further submitted that the right to privacy, as recognised under Article 21, includes decisional autonomy over one's body and personal choices. Any action of the State that interferes with such autonomy must satisfy the requirements of legality, legitimate aim, and proportionality. Administration of any medical treatment without informed consent

amounts to a violation of bodily integrity, physical autonomy, and privacy, and is therefore unconstitutional.

IV. Article 21 of the Constitution guarantees the right to life, which this Hon'ble Court has consistently interpreted to include the right to health and the right to bodily integrity. The mandatory or quasi-mandatory administration of the HPV vaccine to young girls under the UIP, without adequate long-term safety data, without transparent disclosure of adverse event data, and without meaningful informed consent, constitutes a violation of Article 21.

V. The documented serious adverse events including deaths, (POI), postural orthostatic tachycardia syndrome (POTS), complex regional pain syndrome (CRPS), autoimmune disorders impose a real risk of harm on healthy young girls. The State's failure to establish an adverse event surveillance system and compensation mechanism before commencing the rollout is a violation of Article 21.

VI. The right to informed consent is a fundamental component of the right to health and bodily integrity under Article 21, affirmed by the Delhi High Court in Master Haridaan Kumar v. Union of India (2019). The current HPV vaccine rollout does not comply with the standard of informed consent mandated by law. Parents are not being provided with adequate information about the surrogate endpoint basis of approval, the absence of

long-term efficacy data, the documented adverse events, or the conflicts of interest in the approval process.

VII. The precautionary principle recognised in Indian environmental jurisprudence can be inferred as a principle for public health perspective and affirmed by this Hon'ble Court requires that where there are reasonable scientific grounds for believing that a product may cause harm, protective action must be taken before conclusive proof of harm is established. The burden lies on those introducing the product to demonstrate safety, not on the public to prove harm.

VIII. Article 14 prohibits arbitrary State action. However, the whole sequence of events in recommending and approving the HPV vaccine was compromised by undisclosed or inadequately managed conflicts of interest involving senior regulatory officials, ICMR, and non governmental entities The 72nd Parliamentary Standing Committee formally documented these concerns. An approval process tainted by undisclosed conflicts of interest is arbitrary and violates Article 14.

IX. It is submitted that the near absence of organised cervical cancer screening in India, with less than 5% of eligible women being screened, renders the State's decision to prioritise mass HPV vaccination of a large population arbitrary and an unreasonable allocation of public health resources, which may not effectively reduce cervical cancer mortality. Further, in light of Article 21 of the Constitution, which includes the right

to health and bodily integrity, the administration of the HPV vaccine in a mandatory or quasi-mandatory manner, without adequate long-term safety data, transparent disclosure of adverse events, and meaningful informed consent, raises serious constitutional concerns.

X. It is submitted that the absence of a structured no-fault compensation mechanism for vaccine-related adverse events creates a significant gap in the public health framework. The Supreme Court, in *Rachana Gangu v. Union of India*, (2026 INSC 218) has already recognised this issue and directed the formulation of an appropriate policy. However, in the absence of such a mechanism, the process of determining and awarding compensation remains uncertain and difficult, leaving affected individuals without an effective remedy. The need for a uniform compensation framework is therefore essential in the interest of justice and public welfare.

Prayers

In view of the facts and circumstances set out hereinabove, it is most respectfully prayed that this Hon'ble Court may be pleased to:

A. Issue a writ of mandamus or any other appropriate writ, order, or direction directing Respondent No. 1 to forthwith STAY / SUSPEND the mass rollout of the HPV vaccine under the UIP.

B. Issue an appropriate writ, order or direction directing Respondent Nos. 1 to 4 to reconsider and review the decision to include the HPV Vaccine in the Universal Immunisation Programme in light of the concerns relating to efficacy, long-term safety, adverse event monitoring, informed consent.

C. Issue an appropriate writ, order or direction directing the Union of India to formulate and implement a comprehensive No-Fault Vaccine Injury Compensation Scheme for individuals suffering serious adverse events following HPV vaccination

D. Issue an appropriate writ, order or direction directing the Respondents to conduct and publish district-wise and state-wise epidemiological assessments, disease burden studies, cost-effectiveness analyses and public health impact evaluations before any further expansion of the HPV vaccination programme;

E. Issue an appropriate writ, order or direction directing the Respondents to establish and operationalise an independent, transparent and publicly accessible Adverse Events Following Immunisation (AEFI) monitoring and reporting mechanism specifically for HPV vaccination, with periodic public disclosure of all reported adverse events;

F. Pass such other and further order(s) as this Hon'ble Court may deem fit and proper in the facts and circumstances of the case and in the interest of justice.

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NATIONAL CANCER REGISTRY PROGRAMME

Indian Council of Medical Research

Time Trends in Cancer Incidence Rates 1982-2005

Bangalore, India

April 2009

© National Cancer Registry Programme
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April 2009

Population based cancer registries provided individual core data. Quality Control checks, tabulations and statistical analysis were done at the Coordinating Unit of NCRP, Bangalore.

The publications of NCRP are intended to contribute to the dissemination of authentic information on cancer incidence by age (Five-year age groups), sex and site (ICD-10).

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NATIONAL CANCER REGISTRY PROGRAMME

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Staff of Coordinating Unit, NCRP, Bangalore.

FOREWORD

I am pleased to write this foreword for the report on "Time Trends in Cancer Incidence Rates from 1982-2005". ICMR registries have been a major source on type of cancers prevalent in different parts of India. This report covers data for the twenty four year period for the population based cancer registries at Bangalore, Chennai and Mumbai and for an eighteen year period for the registries at Barshi, Bhopal and Delhi.

This is the first report from our country depicting changes in the incidence rates of cancer and is the first for any chronic disease in India. Over the years, the Indian population has seen considerable changes in habits, lifestyle as also variation in the socio-cultural milieu. Advances in cancer diagnostic techniques and treatment facilities have added to the changes. There is an increase in awareness about cancer by the average public.

Against the above background, this scientific information on changing trends in incidence rates of cancer is timely. This data can be useful for planning systemic studies based on specific populations and cohorts. Certain anatomical sites of cancer have shown significant steady increase across all registries, whereas a few other sites have shown a rise in only some registries. Overall there appears a need to redraw priorities towards cancer control, cancer research and patient care.

This report is the culmination of systematic effort by the staff of the population based cancer registries and its principal investigators including those at the Coordinating Unit of the NCRP. All of them deserve special appreciation for the dedicated work of gathering, compiling, analyzing data and preparing this scientific report.



Dr V.M. Katoch
Secretary, Department of Health Research &
Director General, ICMR

PREFACE

The National Cancer Registry Programme (NCRP) was established under the Indian Council of Medical Research in 1981 with the aim of looking at the incidence and distribution of cancer in the country. Three hospital-based and three population-based cancer registries (PBCRs) commenced data collection from 1 January 1982. Three more PBCRs started functioning from 1988. Following the report of the Development of an Atlas of Cancer in India, seventeen other PBCRs have started functioning in more recent years.

The present report depicts Trends in Incidence Rates of Cancer from 1982 for the three older PBCRs and from 1988 for the three PBCRs commenced subsequently. Data collected by the PBCRs are thoroughly checked for quality and completeness before the reports of the respective years are finalized. Despite growing number of cancer centres within the city, every effort is made by the PBCRs to collect information from all sources where cancer is diagnosed and / or treated. The advent and optimal use of Information Technology in capturing and transmitting data is facilitating in improving the data coverage and data quality.

This report has undergone considerable discussions at the Annual Review Meetings of the NCRP and also amongst the various experts in the field. One of the objectives with which the NCRP was commenced was to aid cancer control programmes including the National Cancer Control Programme of India. Though the population covered by the six registries, that go into this publication is small, it does give a fair picture of the direction in which the different anatomical sites of cancer are changing, rising in some instances and declining or stabilising in others.

The results reported are likely to serve as an important resource for multi-institutional research in cancer and its control.



Dr Bela Shah
Head, Division of Non-Communicable Diseases, ICMR

Time Trends in Cancer Incidence Rates : 1982-2005

Executive Summary

Since the commencement of the National Cancer Registry Programme in 1982, annual, bi-annual and consolidated reports have been regularly published. A brief picture on time trends in incidence rates was depicted in the consolidated report for the years 1990-96 *(NCRP, 2001)*. This publication is the first systematic report on trends in incidence rates over a period of about two decades.

The registry data on which the time trends in cancer incidence rates have been depicted, essentially cover urban populations that display rapid life style changes. Diagnostic and detection technologies have increasingly improved since commencement of cancer registration and are now disbursed in several centres in these registry areas. These factors have to be kept in mind while interpreting the results.

There has been a steady and consistent increase in the age adjusted incidence rates of certain cancers across all major urban registries. Such an increase in these specific anatomical sites of cancer, in the light of known risk factors, population dynamics and changing life styles therein is not unexpected. They are also consistent with that observed in the developed world. The anatomical sites that fall into this category are outlined below. Among males, cancers of the prostate, colon, rectum and liver, have shown statistically significant increase in incidence. Cancer of the prostate is the leading site of cancer among males in most of the western countries as is cancer of the colon. Among females, cancers of the breast, corpus uteri and lung have shown a rise. While the first two of these cancers could be accounted for because of cohorts, with later age at marriage, decreasing multi-parity and so on, the increase in lung cancer could directly be attributed to increased use of tobacco smoking by women. Lung cancer in women may also be increasing because of environment exposure to smoking (passive smoking).

Three other sites of cancer that have shown an increase in incidence rates in women are ovary, thyroid and gallbladder. The last is seen in registries that have recorded a comparatively lower incidence than Delhi, which showed an increasing trend only during the earlier years, with a decline in more recent years. Both males and females have recorded rising incidence rates for cancers of the brain as well as in tumours of the lymphoid and haemopoetic system, especially non-Hodgkin's Lymphoma.

While increase in the incidence of cancer over time is along the patterns of that observed for chronic diseases, a decline in incidence rates (with few exceptions) needs explanation and further study.

The decline in the incidence of cancer cervix is seen across all registries including the rural registry at Barshi. This decline is observed in the absence of any organized screening or early detection programmes in the registry areas. The same factors like later age at marriage, fewer children that could be contributing

to increased breast cancer could possibly be responsible for the decline in the incidence of cancer cervix. Another possible reason for the decline could be due to the increased number of child births at institutions (as opposed to home deliveries) culminating in improved maternal and maternity care including genital hygiene. This could be the consequence of the family planning drive initiated by the government about four decades back and which is continuing. Better genital hygiene, barrier contraceptive use, superior nourishment could have all contributed to the reducing incidence of cancer of the cervix.

The decrease in incidence rates of cancer of oesophagus, in both males and females and cancer stomach in males could possibly be due to changes or improved nutrition, better methods of preserving of food etc. Aside from the above, this report does give certain figures that cannot be easily rationalized. The decline in the incidence of lung cancer among males in Mumbai and also in Bhopal especially in more recent years are points to be noted. Similarly, the downward trend in incidence rates during recent years for all anatomical sites combined in males and females in Mumbai and males in Bhopal also requires further study. Such studies would have to include assessment of coverage of cases by sources of registration particularly, because most cities and towns in India have had a spurt in oncology centres including radiotherapy facilities.

The last chapter of this report attempts to project the number of cancer cases by selected leading sites. This is based on the more recent trends in the incidence rates published in this report and the latest two-year *(2005-2006)* report of the six population based cancer registries in the North East of the country *(NCRP, 2008)*. Since the older registries are predominantly urban and the majority of the Indian population is rural, there were complexities in arriving at logical estimates. Nonetheless, this has been worked out and the chapter provides a reasonably accurate burden of cancer.

Priorities for Cancer Control

The cancer registry is central to any rational programme on cancer control *(Muir, 1985)*. With information on trends over time, there appears to be a need for reassessing priorities for cancer control. The overall thrust of the cancer control programme towards anti tobacco education / legislation and control of cancer cervix is largely unchanged. However, certain specific pointers emerge from this report.

The rate of increase in the incidence of cancer of the lung among women is glaring calling for systematic evidence based and focused anti-tobacco campaigns targeting the urban woman. Two other cancers in women that are increasing and for which, promotion of awareness for early detection is required are cancers of the breast and corpus uteri.

Among males, nationwide screening programmes for cancer of the prostate, colon and rectum are essential.

While control of tobacco use has to be constantly emphasised, the importance of obesity control and genital hygiene could be propagated. The necessity for early detection should be increasingly highlighted along with public education and self examination methods. The role of registries would ultimately be made applicable with overall trend studies as well as trends of stage at disease presentation.

Priorities for anatomical site specific Cancer Research

In the present background, cancer research could comprise epidemiological research, basic laboratory research or cancer control research or a combination of these. Risk factors, such as tobacco and its association with specific anatomical sites of cancer are well known. However, in the Indian context some of the tobacco habits (like types of tobacco chewed, beedi smoking) vary in different parts of the country and India specific tobacco related cancer research is required. Besides, this report has shown several specific sites of cancer that are rising in incidence rates. These are cancers of the prostate, colon, rectum and liver in men and thyroid & gallbladder in women. In both sexes, tumours of the brain and nervous system and the lymphoid and haemopoietic malignancies have shown a rise. This calls for systematic epidemiological research preferably taking into account laboratory parameters for each of these sites of cancer. One of the outstanding features noted relate to the contrasting incidence of certain cancers in relation to geographic locations. Cancers of the gall bladder and thyroid are prominent examples. These provide unique opportunities for multi-centric case control studies which have to be systematized now.

Similarly, there are no definitive directly replicable models for early detection / screening of cancers of the thyroid, gall bladder, rectum, liver, ovary and corpus uteri. The first four sites are country specific and research into various modules for cancer control need to be done.

Priorities for anatomical site specific Clinical Research

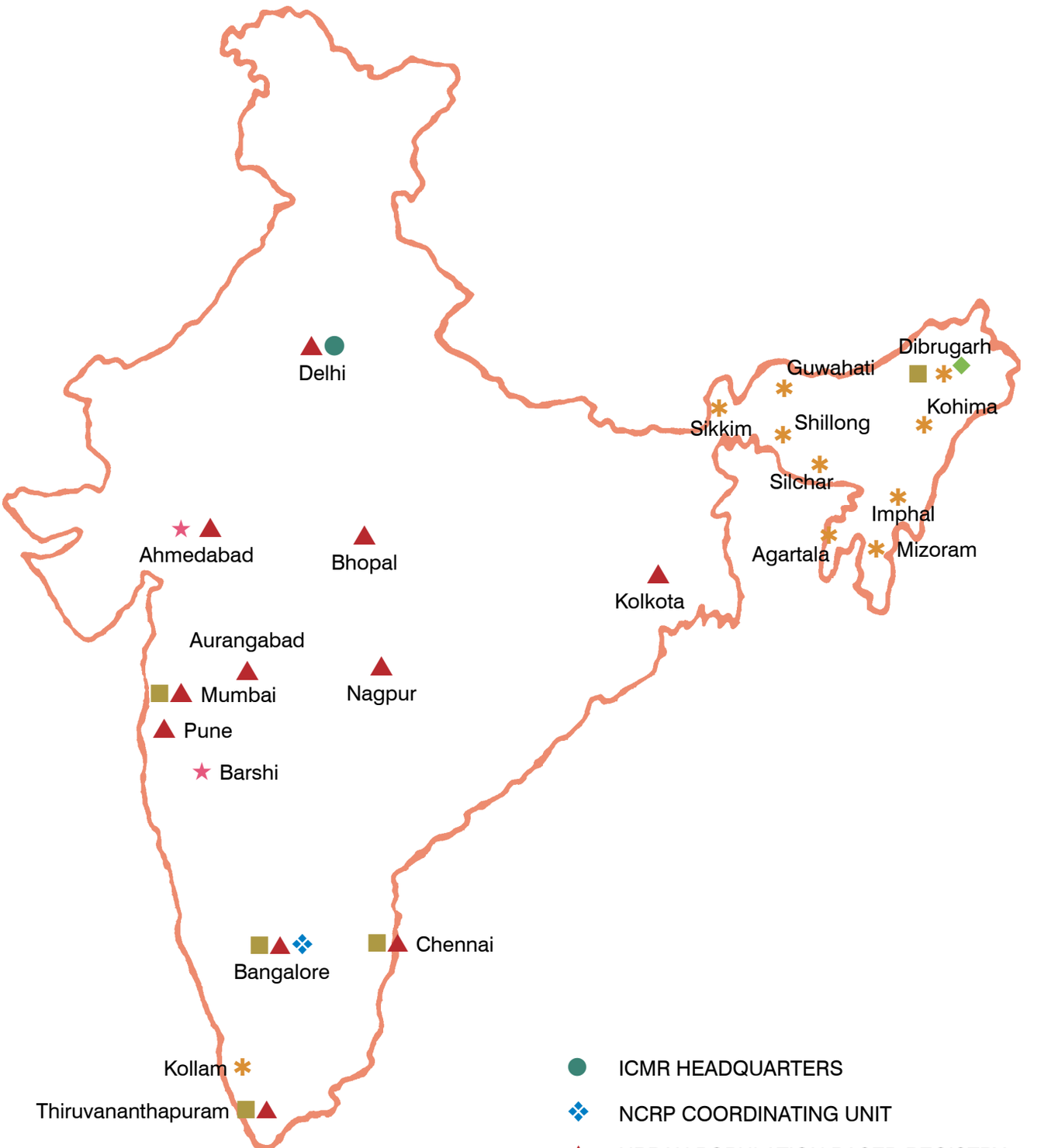
There are international and standard guidelines for clinical staging and protocols for treatment of most cancers, including the ones that are showing an increase in this report. Their applicability in our settings needs detailed studies and investigations. This seems particularly important for cancers of the prostate, colon and rectum in men and for cancers of the breast, ovary, corpus uteri and thyroid in women.



Dr A. Nandakumar
Officer-in-Charge, NCRP

NATIONAL CANCER REGISTRY PROGRAMME

(Indian Council of Medical Research)



Chapter 1

INTRODUCTION

A common question of interest is “Is Cancer on the Rise?”. Cancer is known to be a disease that increases in incidence with increasing age. Control of communicable diseases, has increased life expectancy and therefore exposed more of the population towards the development of cancer. The increase in population due to growth also contributes to the increase in the number of cancer cases. Improved literacy, greater consciousness about health in general and awareness about cancer in particular makes more and more people seek medical advice at an earlier stage. Availability of sophisticated and improved diagnostic techniques aid in detection of tumours that would have been missed at earlier times. The question is whether cancer is on the increase after accounting for these factors and whether that rise is statistically significant.

One measure of determining such an increase would be to examine the age adjusted incidence rates (AAR) over time. This may or may not take into account all of the factors mentioned above. Nonetheless, it would give some indication of the trends in the disease. Cancer being a chronic disease (and unlike infectious diseases) with generally a long latent period and a rather prolonged clinical phase, year to year variations are slight. Therefore, in assessing time trends in AAR, the normal practice in registries across the world is to look at five yearly rates over decades. This would give a more definitive indication of the course of the disease. Nonetheless, the data presented here gives a fair account of the direction in which the incidence rates of the leading sites of cancer are proceeding across the years. Based on this, the report also provides an estimate of the burden of specific sites of cancer for the next decade. Such estimates will greatly facilitate deciding on priorities and planning site specific cancer control activities.

Cancer of the Corpus Uteri showed an increase in incidence rates in the four metros. The Annual Percentage Change (APC) was 5.8 in Bangalore and 3.8 in Delhi.

The Annual percentage of increase in cancer prostate in Chennai was 4.7 and 3.1 in Delhi.

In Chennai and Bangalore both males and females showed an increase in brain tumours. The annual percentage change was highest in Chennai females with an APC of 4.6.

Chapter 2

MATERIALS AND METHODS

The numerator data of all registries has undergone a series of range and consistency checks each year and again before preparing this report. Clarifications were sought wherever required from the respective PBCRs and the data finalised thereafter.

The difference distribution method *(Takiar & Shobana, 2009)* for estimating the calendar year wise denominator population by five year age group has been used. This was based on the census data of 1981, 1991 and 2001.

In determining the significance of trends, the actual value of the AAR rate for each year has been used. The significance of time trend in each PBCR was assessed based on the methods and formula provided by Boyle and Parkin, 1991 in the chapter from the IARC publication on Cancer Registration. In addition, the Joinpoint Regression Program of the NCI of USA has been used *(Kim et al, 2001)*.

About Joinpoint Regression Program:

Joinpoint Regression Program, Version 3.0, is statistical software for the analysis of trends using Joinpoint models, that is, where several different regression lines are connected together at the "Joinpoints". Cancer trends reported in NCI publications are calculated using the Joinpoint Regression Program to analyze rates calculated by the SEER. The software takes trend data (e.g. cancer rates) and fits the simplest Joinpoint model that the data allow. The user supplies the minimum and maximum number of Joinpoints. The program starts with the minimum number of Joinpoint (e.g. 0 Joinpoint, which is a straight line) and tests whether more Joinpoints are statistically significant and must be added to the model (upto that maximum number). This enables the user to test that an apparent change in trend is statistically significant. The tests of significance use a Monte Carlo Permutation method. The models may incorporate estimated variation for each point (e.g. when the responses are age adjusted rates) or use a Poisson model of variation. In addition, the models may also be linear on the log of the response (e.g. for calculating annual percentage rate change). The software also allows viewing one graph for each Joinpoint model, from the model with the minimum number of Joinpoints to the model with the maximum number of Joinpoints (Kim et al, 2001). For the report purposes, one Joinpoint model wherever feasible has been fitted to the data. It may be pointed out that whenever a strong linear trend exists in the data the one Joinpoint model results will tally exactly with that of linear regression method.

This report is based on the data of six PBCRs – viz., Bangalore, Barshi, Bhopal, Chennai, Delhi and Mumbai. For the PBCRs at Bangalore, Mumbai and Chennai, the data available is from 1982. Accordingly, the trend in AAR over time is for the 24 year period from 1982 to 2005. The PBCRs at Barshi, Bhopal and Delhi commenced from 1988. Accordingly, the time trend is for the 18 year period from 1988 to 2005.

While depicting the results of specific anatomical sites of cancer in chapter 4, those sites with fewer than 10 cases for any given year have been excluded. This is mostly seen in the case of Barshi and Bhopal PBCRs and in sites of cancer other than the first five or six leading sites.

Among males, cancers of the prostate, colon, rectum and liver, have shown statistically significant increase in incidence. Cancer of the prostate is the leading site of cancer among males in most of the western countries as is cancer of the colon. Among females, cancers of the breast, corpus uteri and lung have shown a rise.

Both males and females have recorded rising incidence rates for cancers of the brain as well as in tumours of the lymphoid and haemopoetic system, especially non-Hodgkin's Lymphoma.

Three other sites of cancer that have shown an increase in incidence rates in women are ovary, thyroid and gallbladder.

Among males in Bangalore, during 1982–83, stomach was the leading site of cancer and it continues to be so twenty four years down the line. In females in Bangalore, cancer of the lung that did not appear among ten leading sites in 1982-83 is the tenth leading site during 2004-05.

In males in Bhopal, cancer of the lung and mouth were the first and third leading sites earlier and have become the first two leading sites in 2004-05.

In males in Chennai, stomach was the leading site of cancer during 1982-83 and this site has been replaced by lung in more recent years.

Chapter 3

INDIVIDUAL REGISTRY - LEADING SITE GRAPHS

The following bar graphs provide the comparison of the leading sites of cancer for the first two years of registry operation and the recent two years data. This will be 1982–83 and 2004–05 for the PBCRs at Bangalore, Mumbai and Chennai and 1988-89 and 2004-05 for the registries at Barshi, Bhopal and Delhi.

Bangalore (Figure 3.1(a) & 3.1(b)) :

Males: Among males, during 1982–83, stomach was the leading site of cancer and it continues to be so twenty four years down the line. Cancer of the prostate was the tenth leading site in the earlier years and is now the fourth leading site. Cancers of the brain and colon that were not, are now among ten leading sites in 2004–05.

Females: Among females, cancer of the breast has replaced cancer of the cervix as the leading site. Cancers of the corpus uteri and ovary have increased in their ranking. Cancer of the lung that did not appear among ten leading sites in 1982-83 is the tenth leading site during 2004-05.

Barshi (Figure 3.2(a) & 3.2(b)) :

Males*:* Cancers of the hypopharynx and oesophagus continue to be the first two leading sites among males in Barshi. Cancer of the brain has appeared among the leading sites of cancer as also non-Hodgkin's Lymphoma (NHL).

Females: Among females, cancer of the cervix uteri continues to be the leading site. Cancer of the lung has appeared as the fifth leading site during 2004-05.

The data from Barshi is in relatively small numbers because of the smaller geographic area covered. Therefore, caution needs to be observed in interpreting this data.

Bhopal (Figure 3.3(a) & 3.3(b)) :

Males: Cancer of the lung and mouth were the first and third leading sites earlier and have become the first two leading sites in 2004-05. Cancer of the prostate has increased in ranking. The new sites of cancer that have appeared among the ten leading sites during 2004-05 are non-Hodgkin's Lymphoma, liver and myeloid leukaemia.

Females: Among females, as in other urban registries, cancer of the breast has replaced cancer of the cervix as the leading site of cancer and cancer of the ovary has risen in rank as the third leading site.

Chennai (Figure 3.4(a) & 3.4(b)) :

Males: Stomach was the leading site of cancer during 1982-83 and this site has been replaced by lung in more recent years. Cancers of the prostate and rectum have appeared as the seventh and tenth leading site of cancer. These sites were not seen among ten leading sites during 1982-83.

Females: Among females, cancer of the breast has replaced cancer of the cervix as the first leading site of cancer. Cancer of the ovary which was the fifth leading site earlier has gone up in rank. Cancer of the lung with brain and corpus uteri have appeared as the eighth and ninth leading sites of cancer during 2004-05.

Delhi (Figure 3.5(a) & 3.5(b)) :

Males*:* Cancer of the lung was and is the leading site of cancer among males. Cancer of the prostate which was the eighth leading site during 1988-89 has become the second leading site during 2004-05.

Females: Cancer of the breast has replaced cancer of the cervix as the leading site. Cancer of the ovary and gall bladder continue to be the third and fourth leading sites. Cancer of the corpus-uteri which was the tenth leading site has become fifth leading site of cancer. Cancer of the lung was not among the ten leading sites during 1988-89 has become sixth leading site during 2004-05.

Mumbai (Figure 3.6(a) & 3.6(b)) :

Males: Cancer of the lung continues to be the leading site of cancer. Cancer of the prostate which was the eighth leading site has now become the third leading site of cancer. Cancer of the brain which was not among ten leading sites during 1982-83 has become the tenth leading site of cancer.

Females: Cancer of the breast continues to be the leading site of cancer for almost a quarter of a century. Cancers of the ovary, lung and corpus uteri have gone up in their ranking.

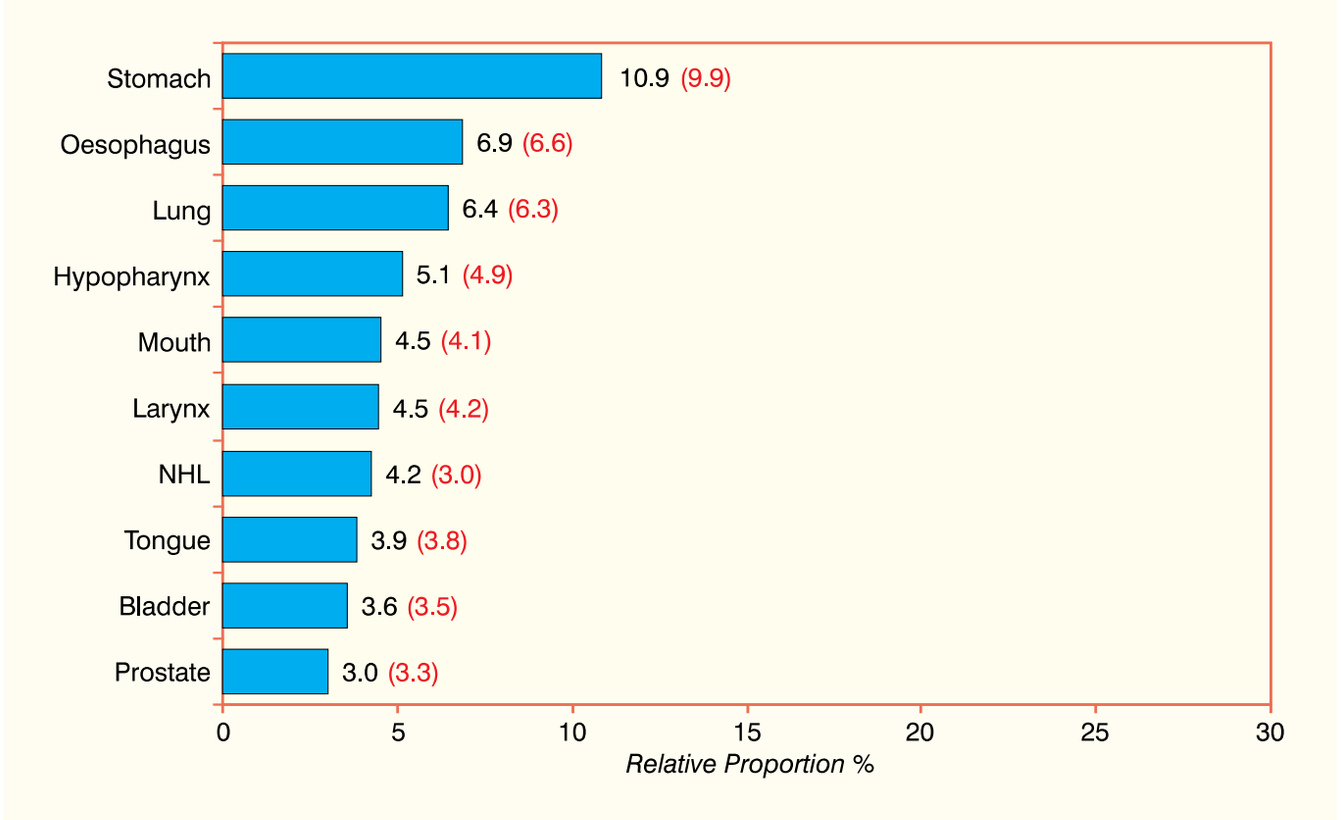
In males in Delhi, cancer of the prostate which was the eighth leading site during 1988-89 has become the second leading site during 2004-05. In females in Delhi, cancer of the breast has replaced cancer of the cervix as the leading site. Cancer of the ovary and gall bladder continue to be the third and fourth leading sites. Cancers of the corpus-uteri which was the tenth leading site has become fifth leading site of cancer. Cancer of the lung was not among the ten leading sites during 1988-89 has become sixth leading site during 2004-05.

In males in Mumbai, cancer of the prostate which was the eighth leading site has now become the third leading site of cancer.

Fig. 3.1(a): Ten Leading Sites of Cancer – Males : Bangalore

Age Adjusted Incidence Rates given in parentheses

1982-1983



2004-2005

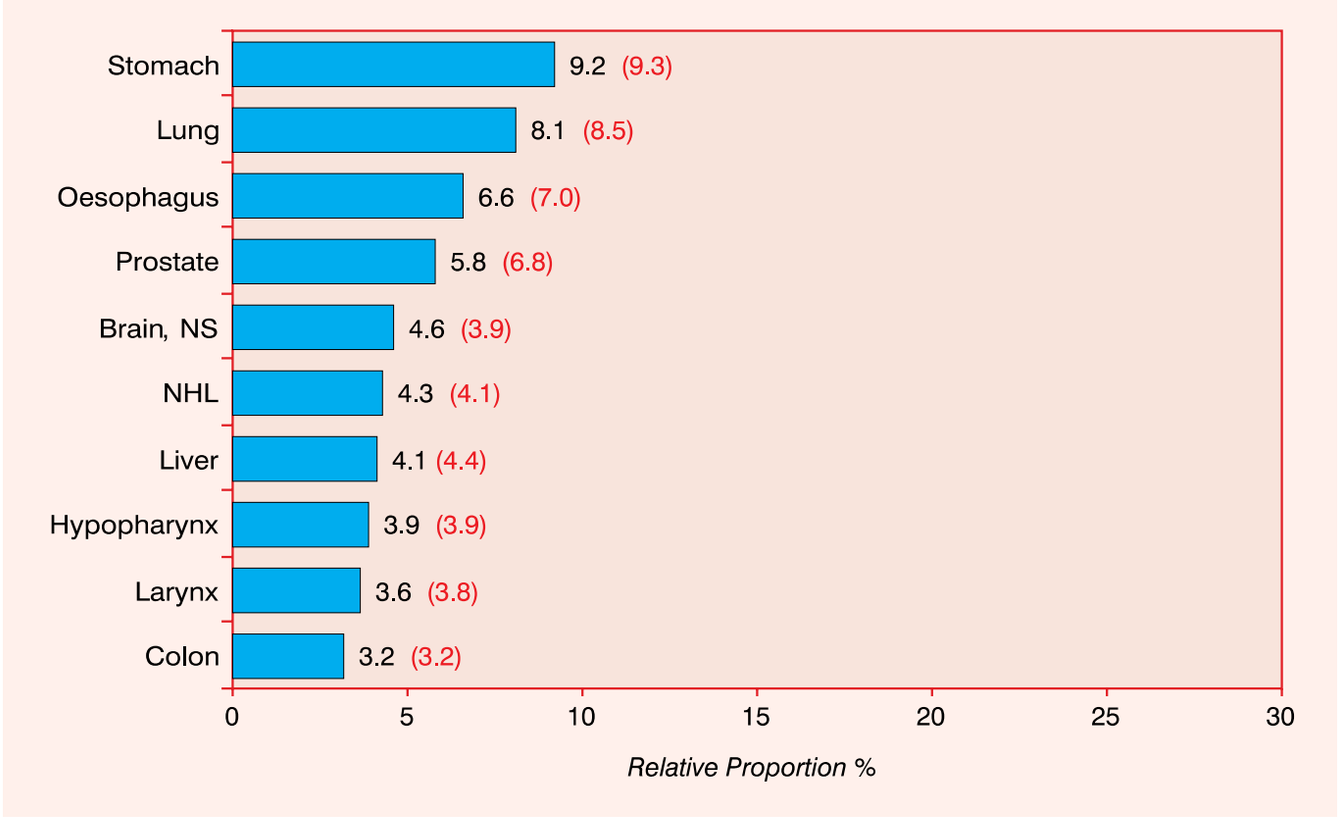
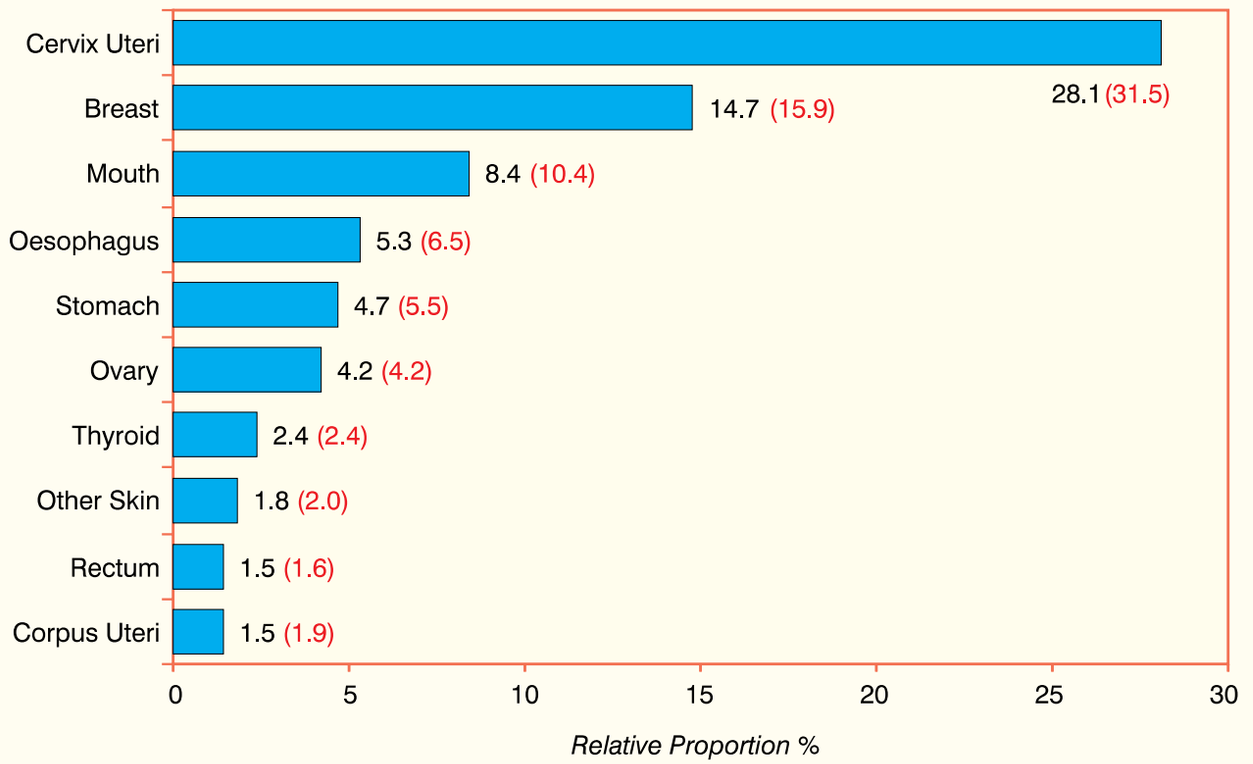


Fig. 3.1(b): Ten Leading Sites of Cancer – Females : Bangalore

Age Adjusted Incidence Rates given in parentheses

1982-1983



2004-2005

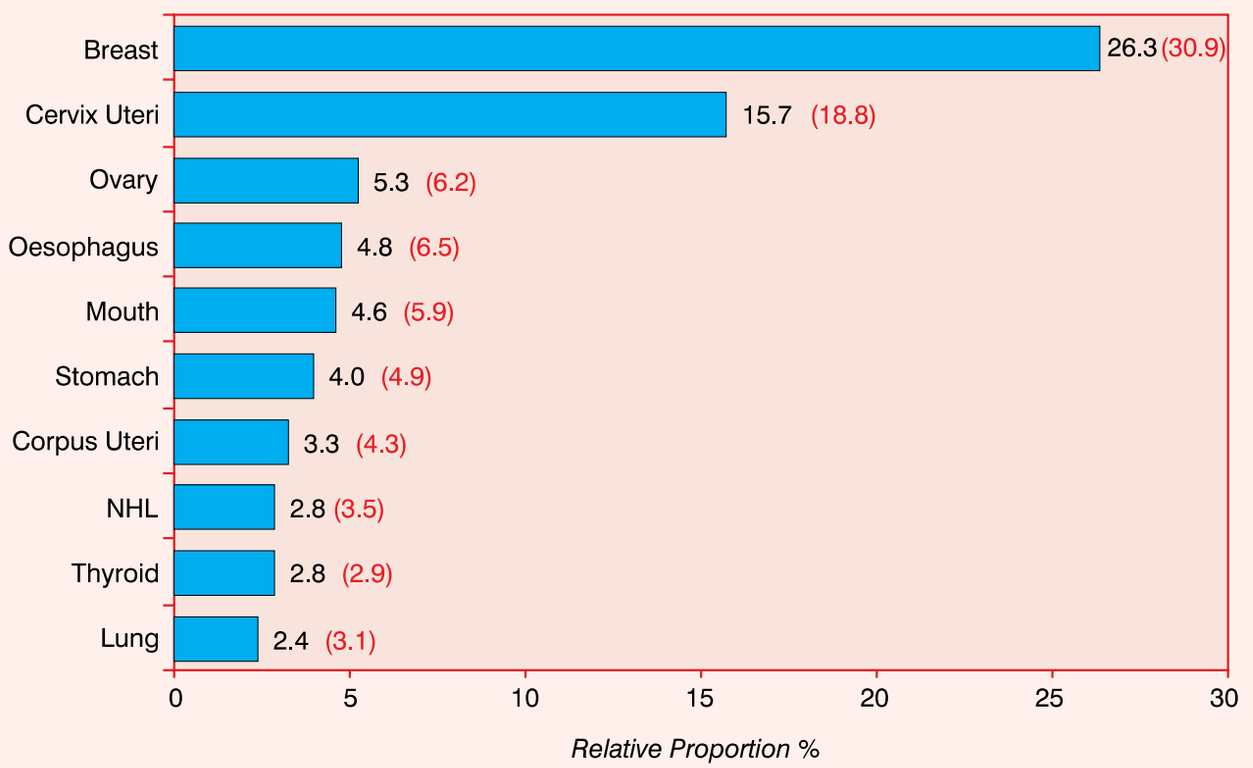
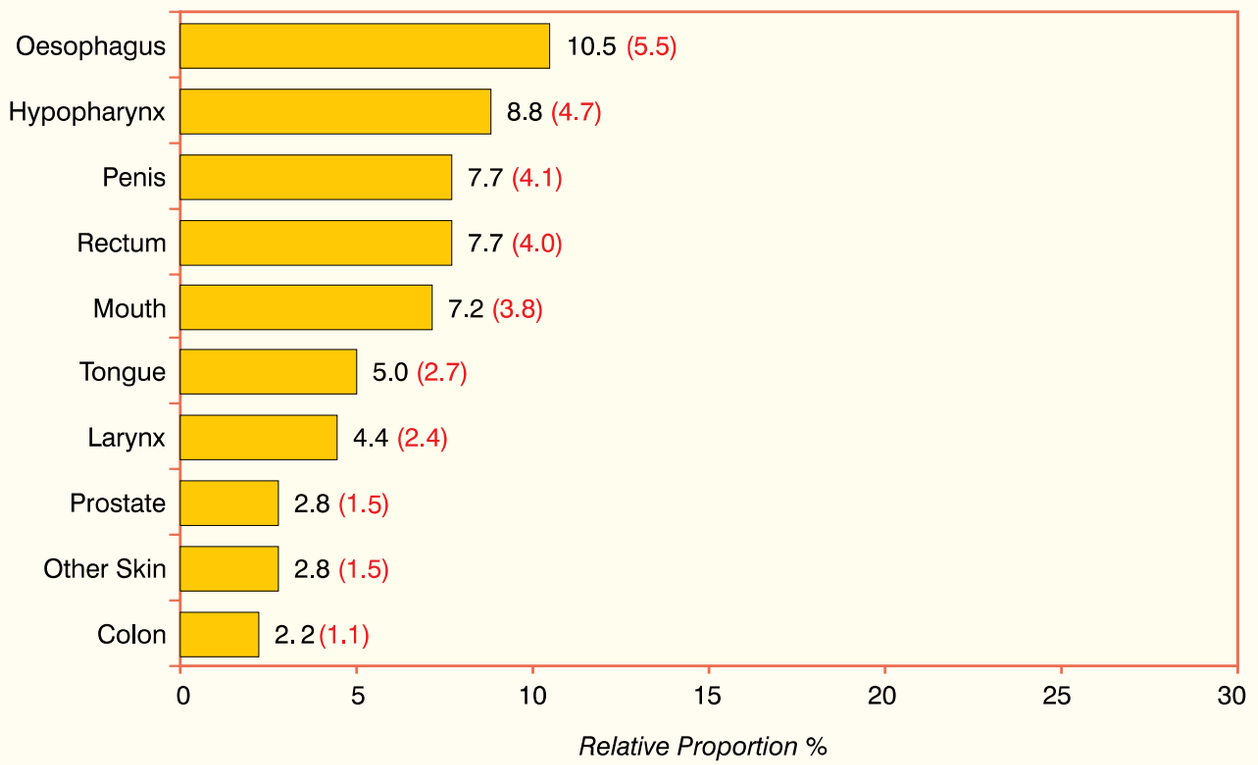


Fig. 3.2(a): Ten Leading Sites of Cancer – Males : Barshi

Age Adjusted Incidence Rates given in parentheses

1988-1989



2004-2005

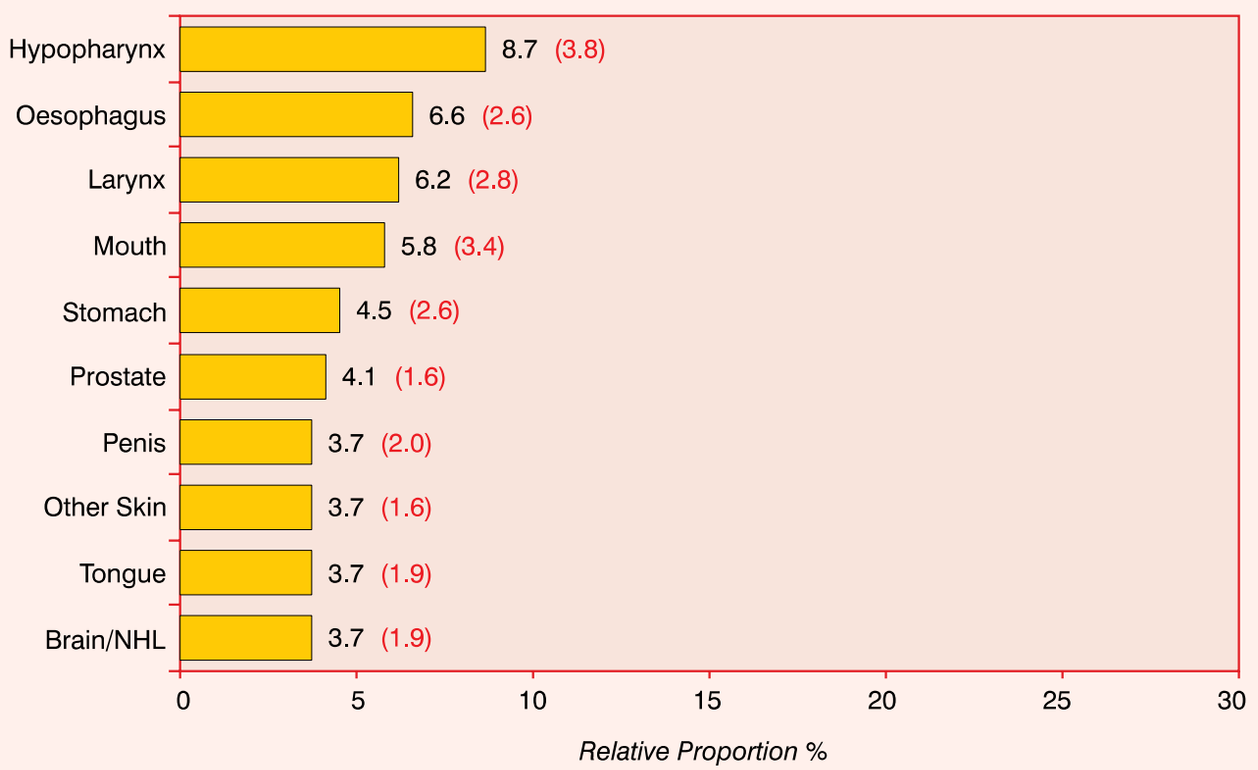
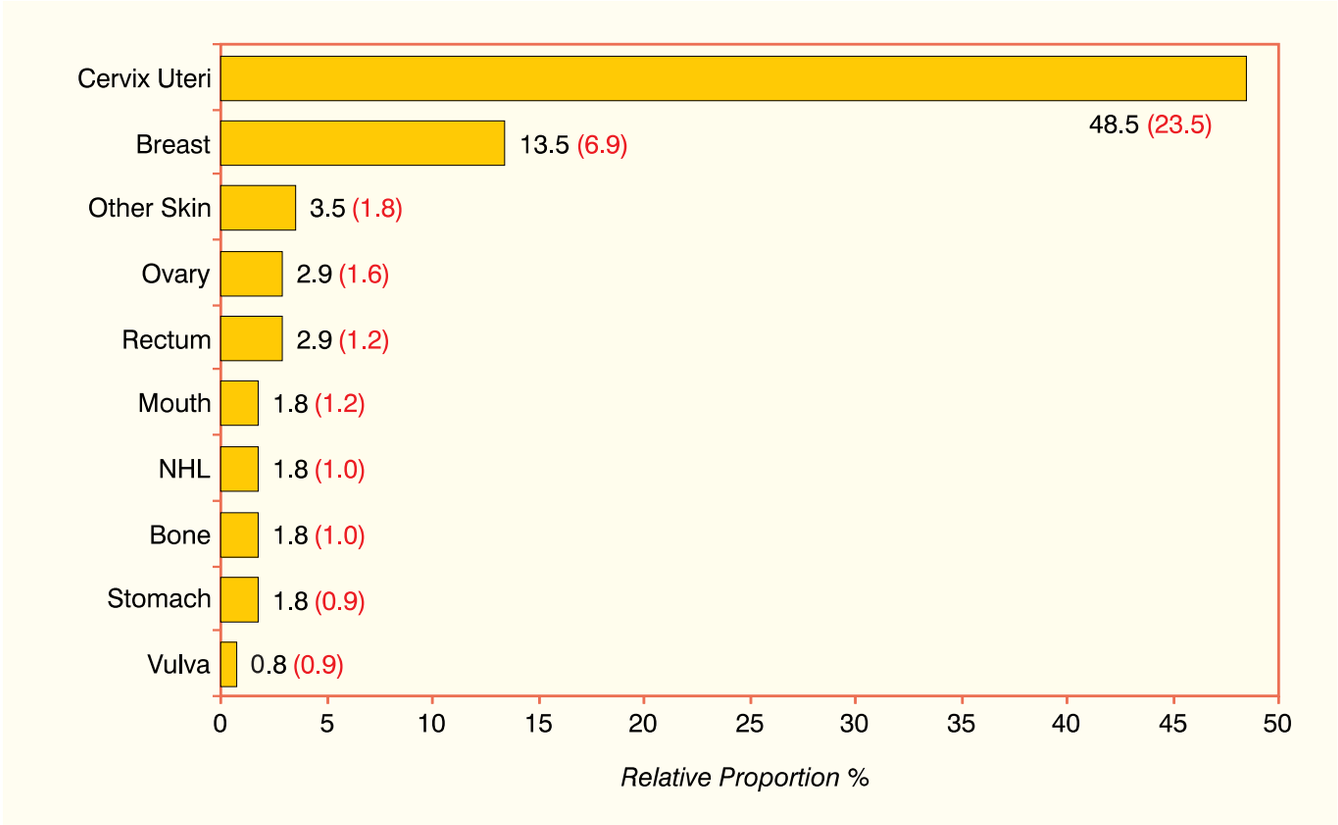


Fig. 3.2(b): Ten Leading Sites of Cancer – Females : Barshi

Age Adjusted Incidence Rates given in parentheses

1988-1989



2004-2005

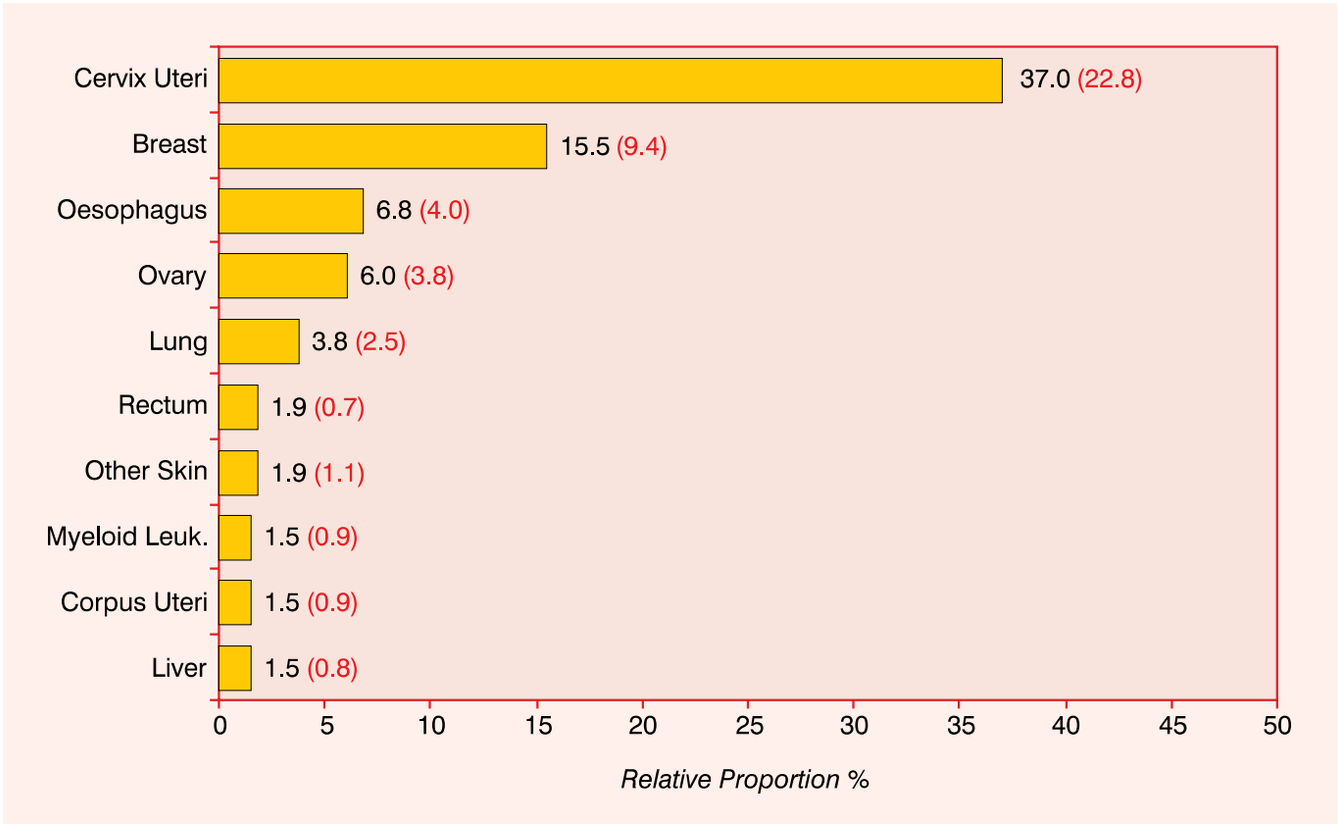
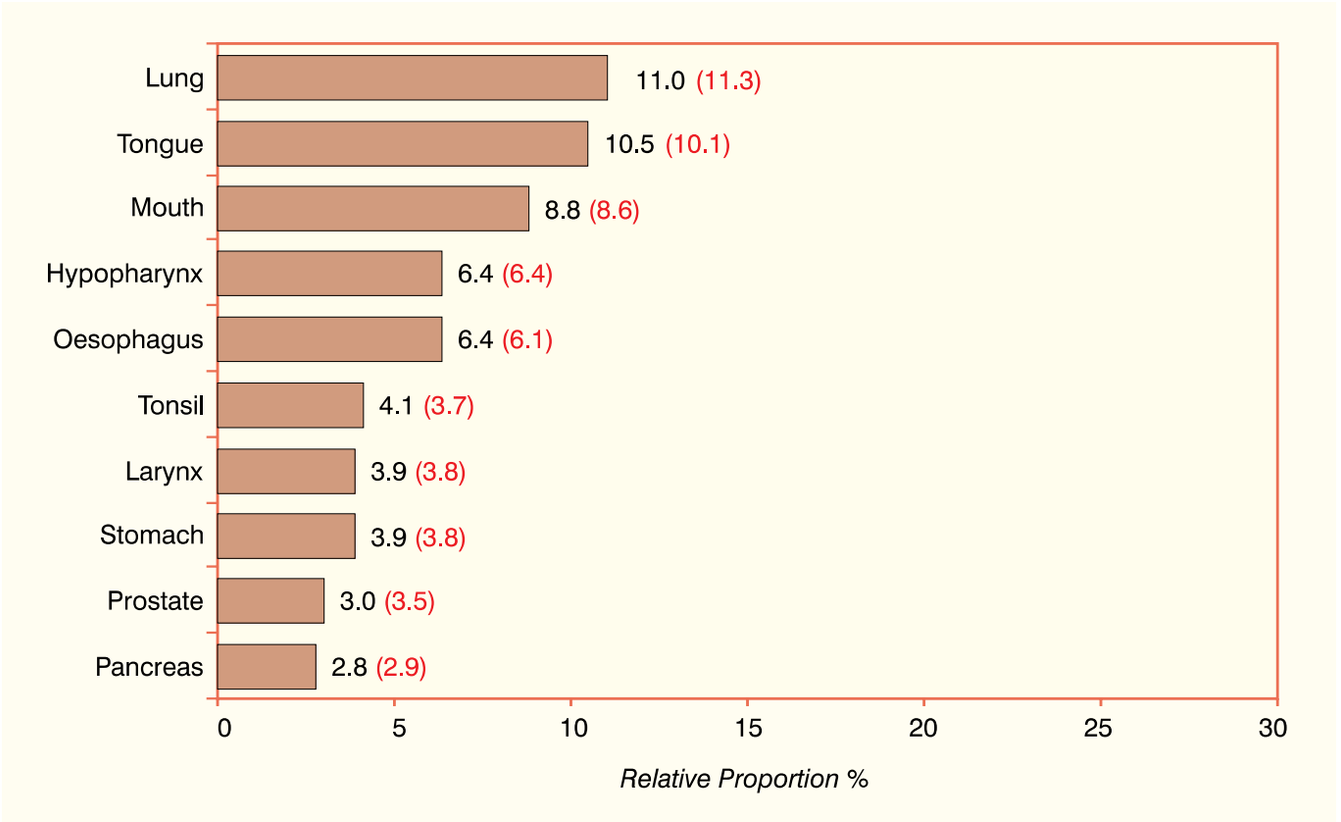


Fig. 3.3(a): Ten Leading Sites of Cancer – Males : Bhopal

Age Adjusted Incidence Rates given in parentheses

1988-1989



2004-2005

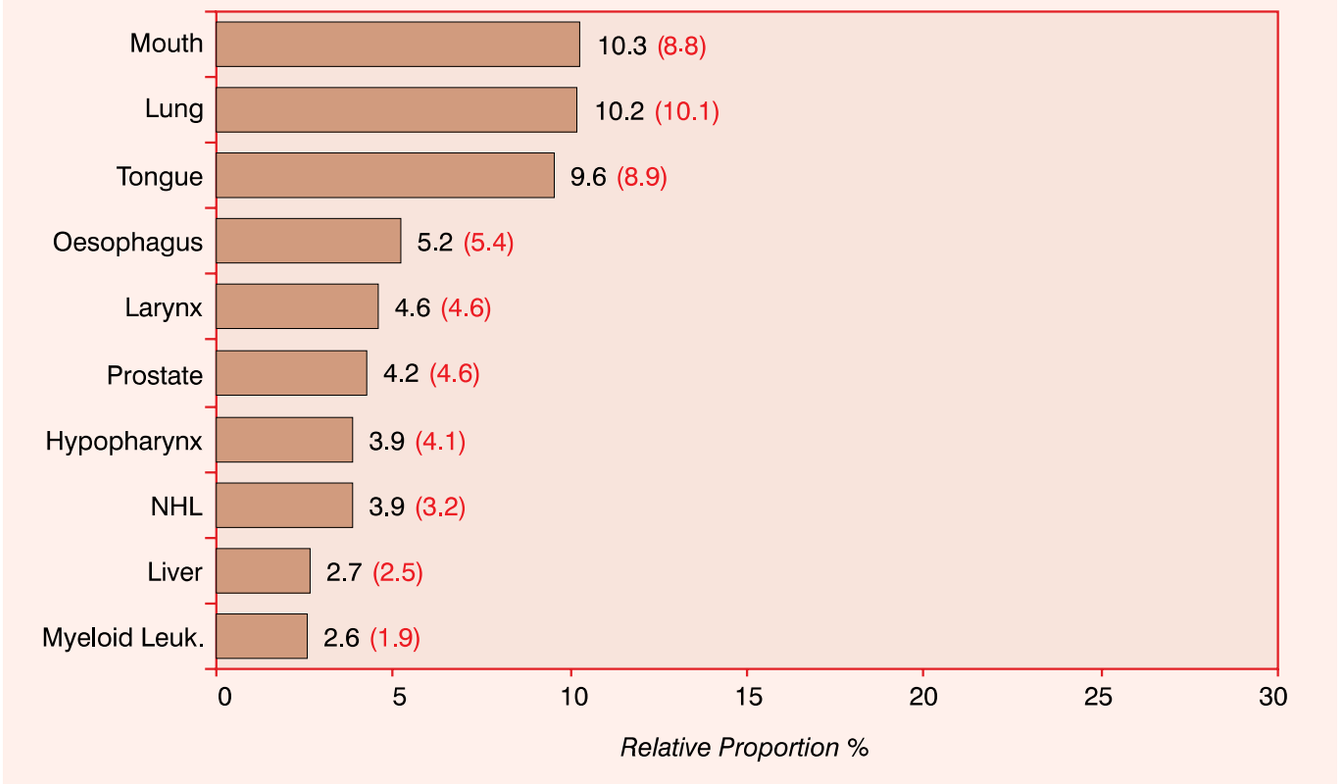
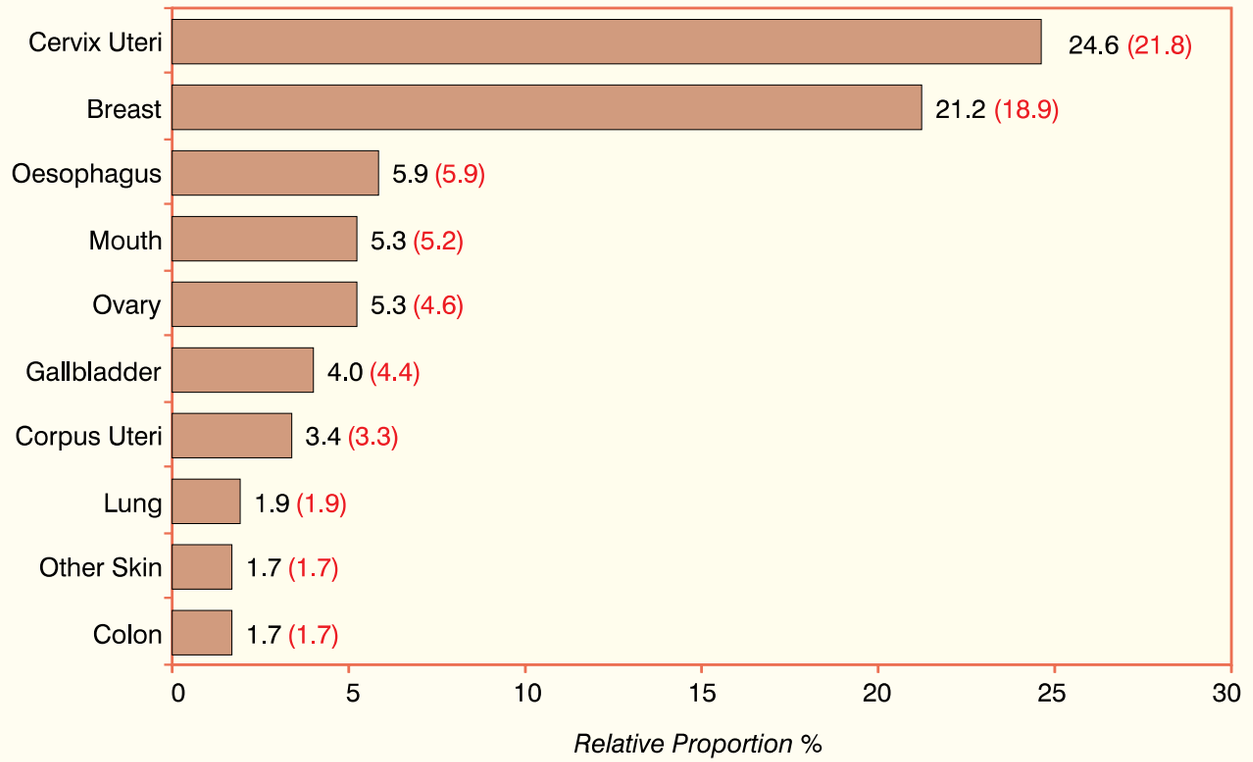


Fig. 3.3(b): Ten Leading Sites of Cancer – Females : Bhopal

Age Adjusted Incidence Rates given in parentheses

1988-1989



2004-2005

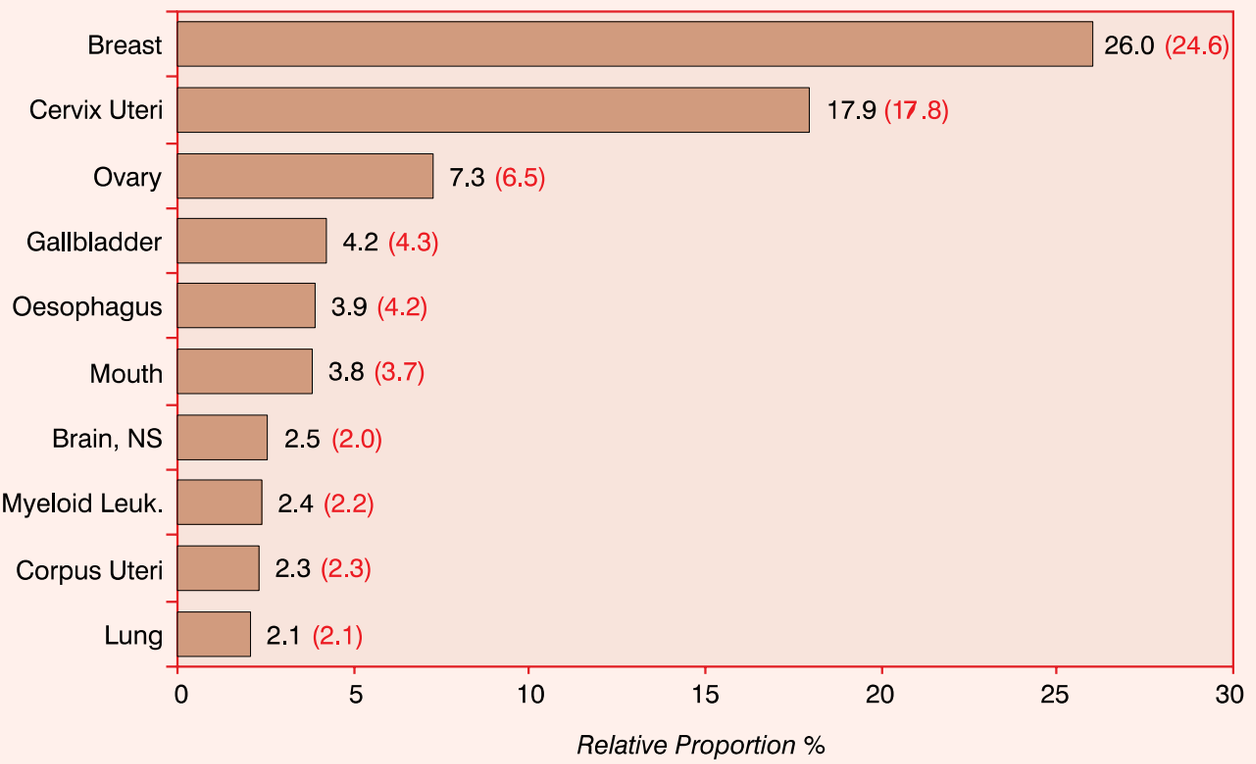
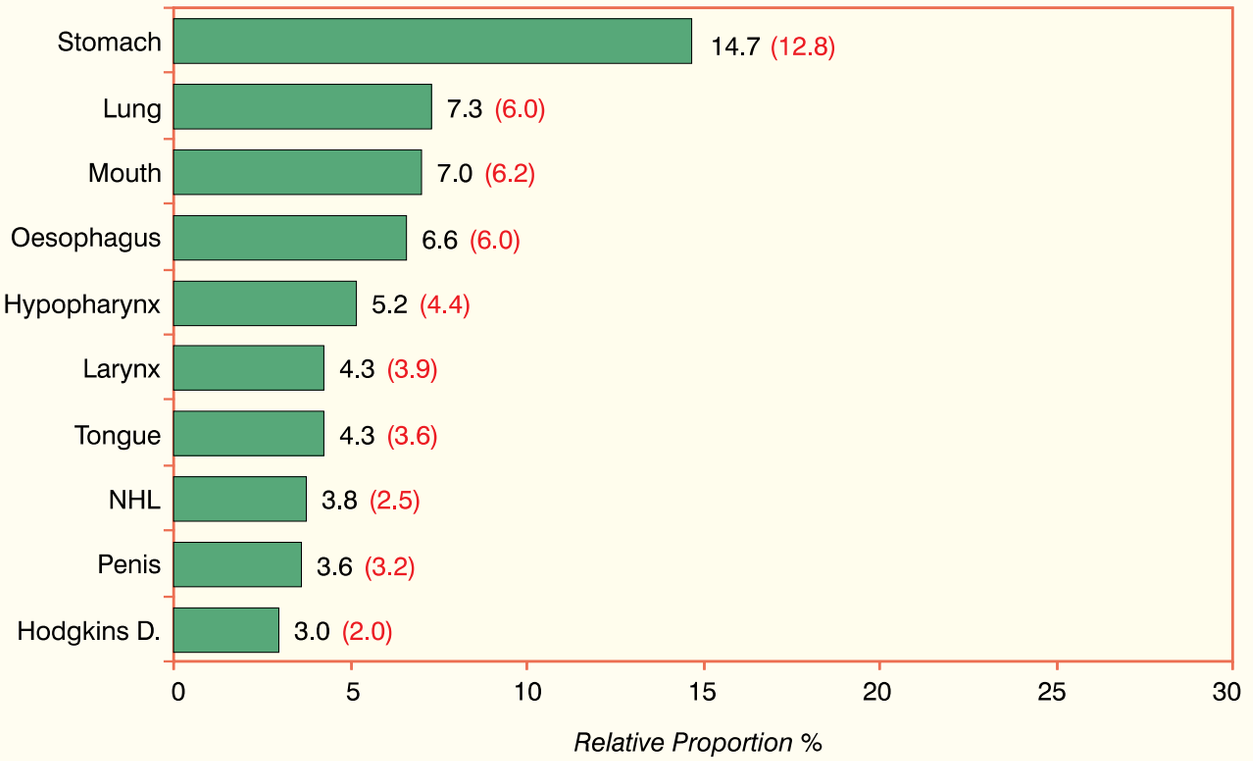


Fig. 3.4(a): Ten Leading Sites of Cancer – Males : Chennai

Age Adjusted Incidence Rates given in parentheses

1982-1983



2004-2005

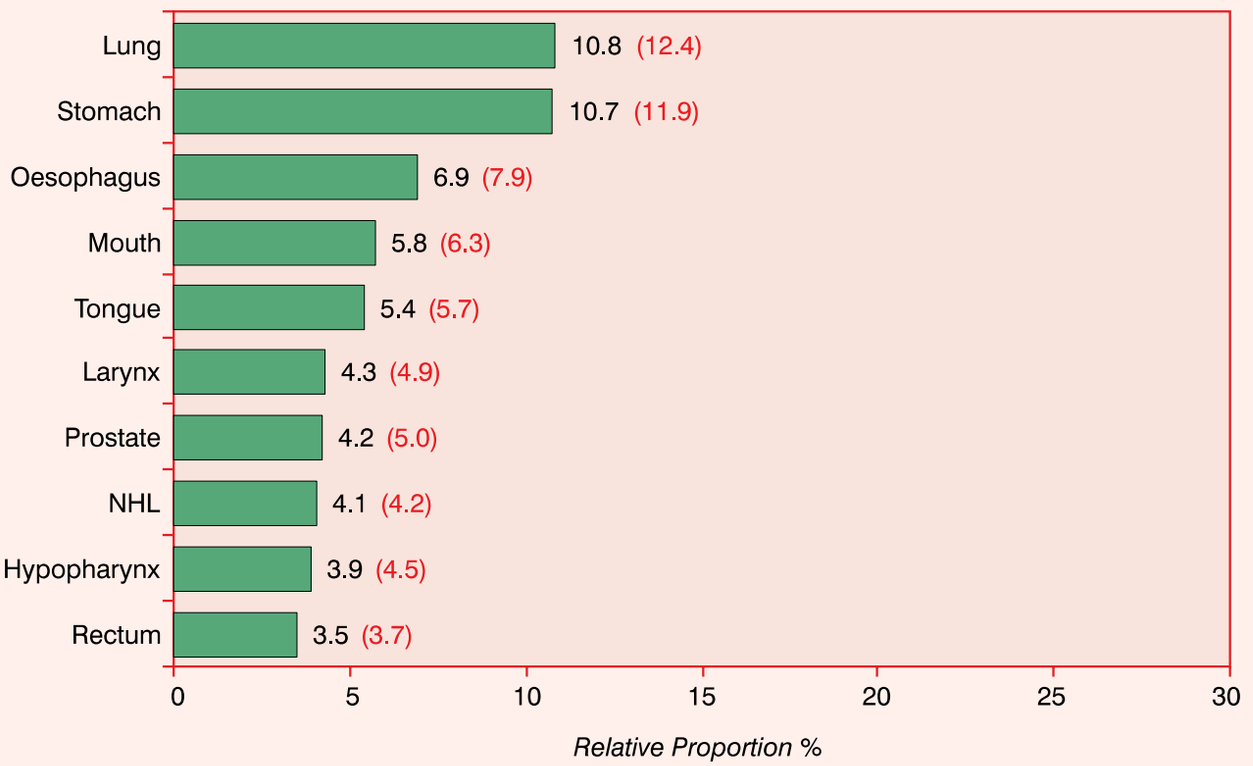
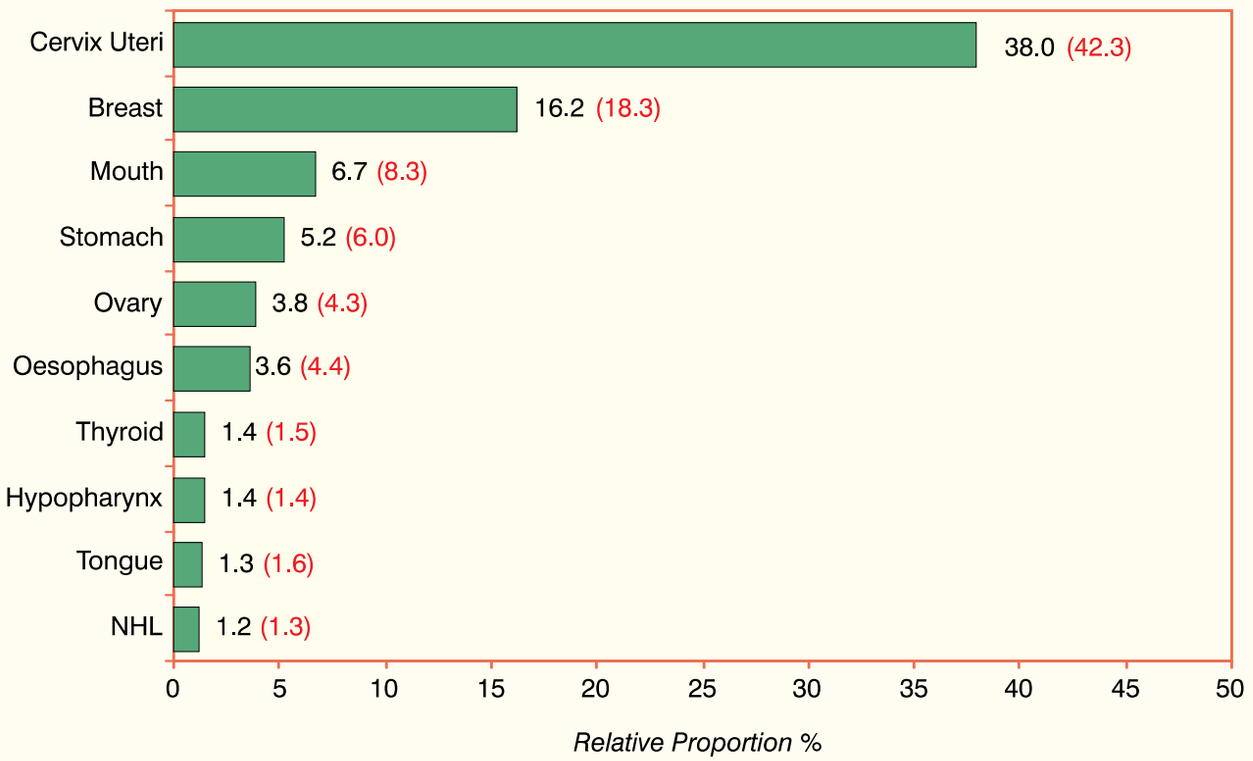


Fig. 3.4(b): Ten Leading Sites of Cancer – Females : Chennai

Age Adjusted Incidence Rates given in parentheses

1982-1983



2004-2005

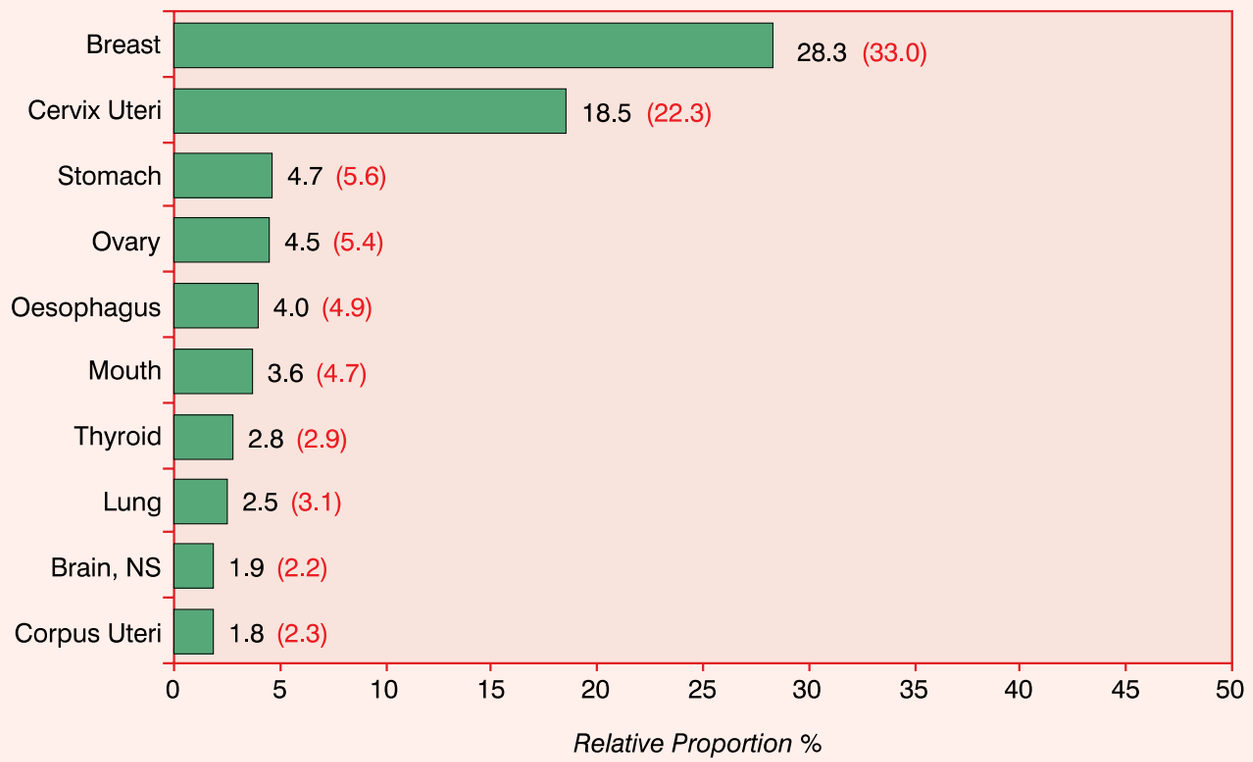
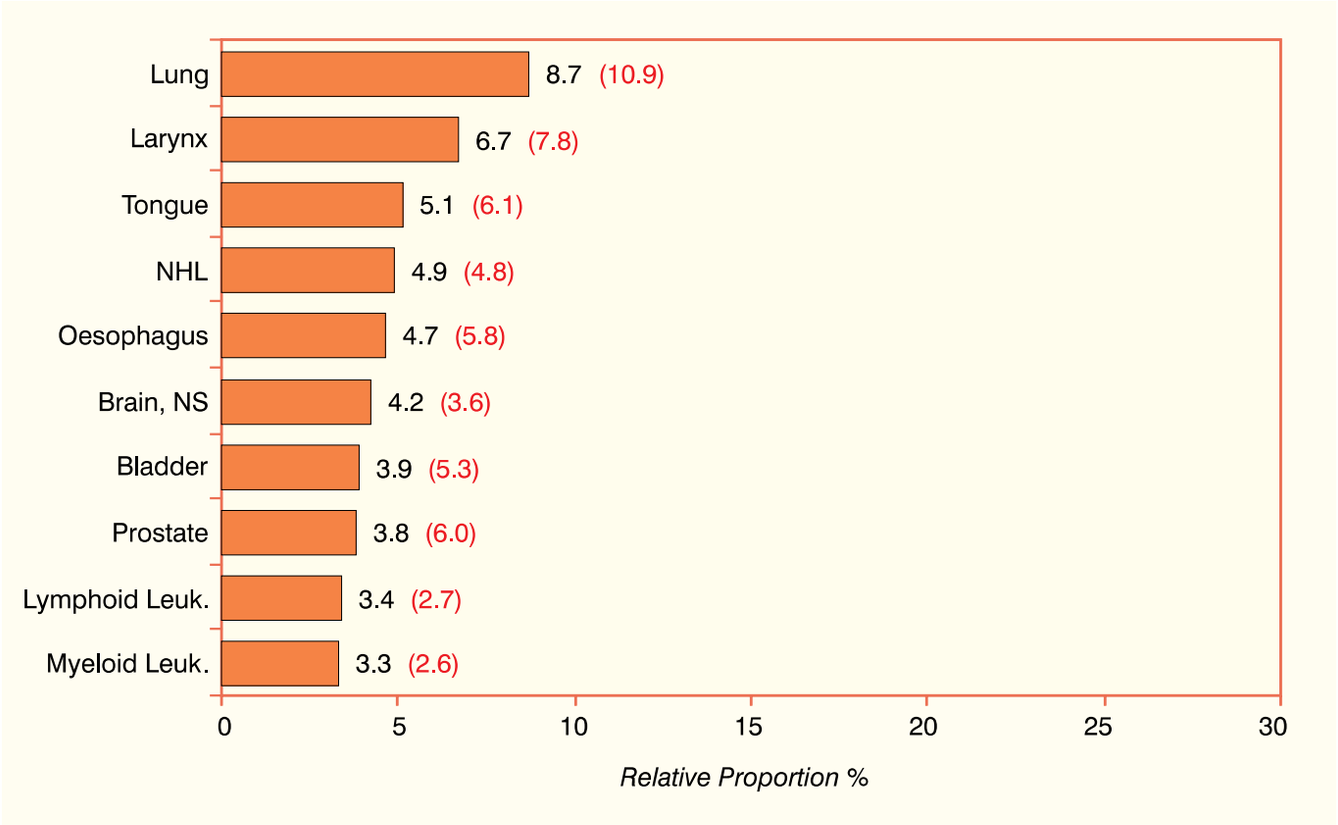


Fig. 3.5(a): Ten Leading Sites of Cancer – Males : Delhi

Age Adjusted Incidence Rates given in parentheses

1988-1989



2004-2005

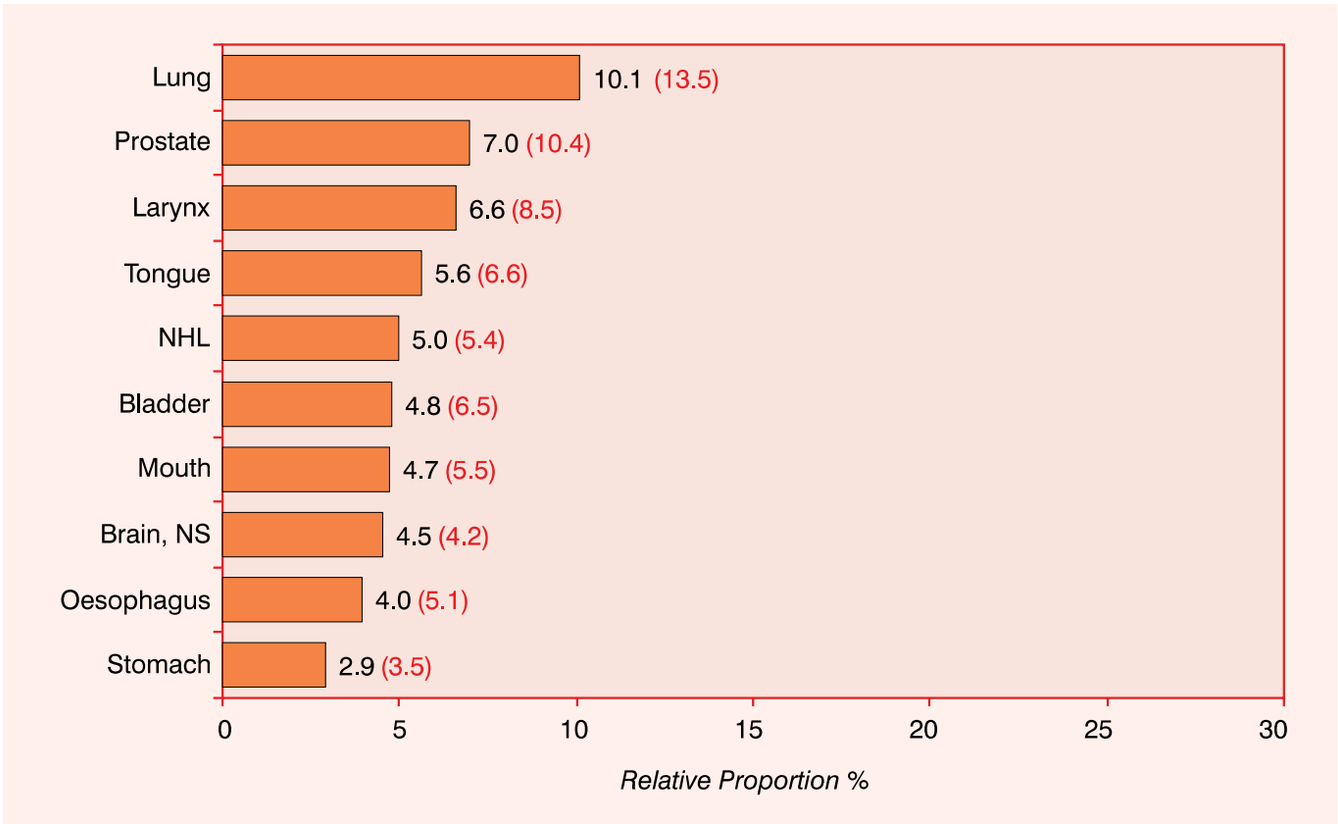
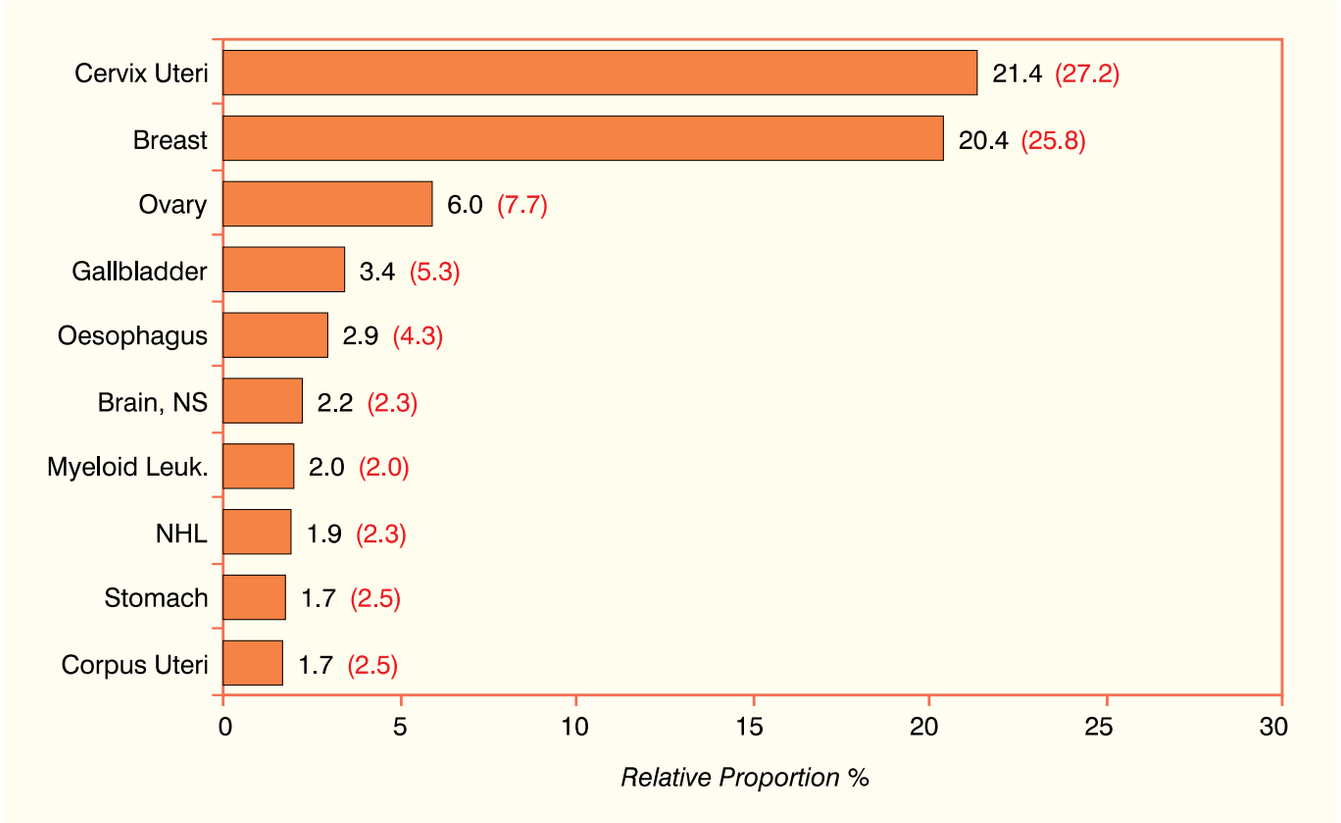


Fig. 3.5(b): Ten Leading Sites of Cancer – Females : Delhi

Age Adjusted Incidence Rates given in parentheses

1988-1989



2004-2005

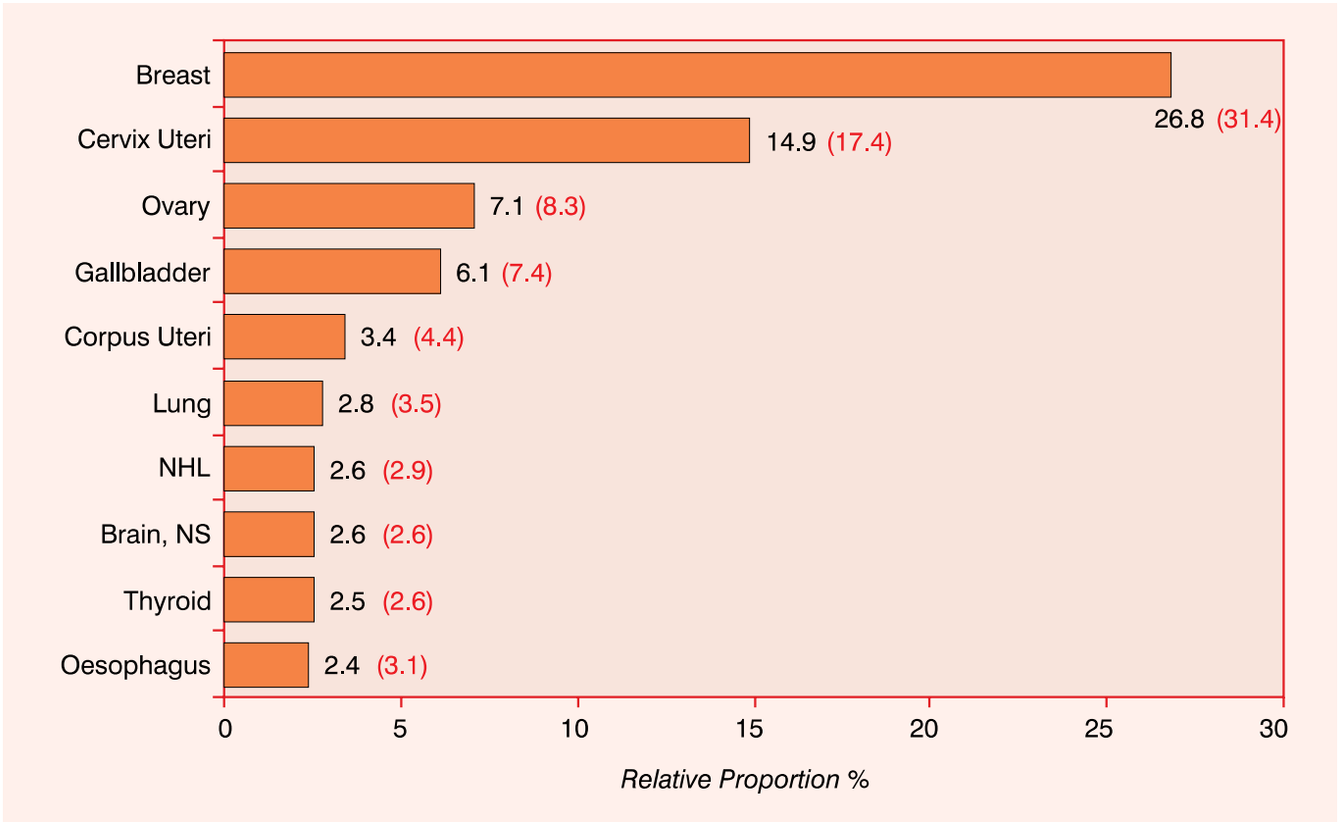
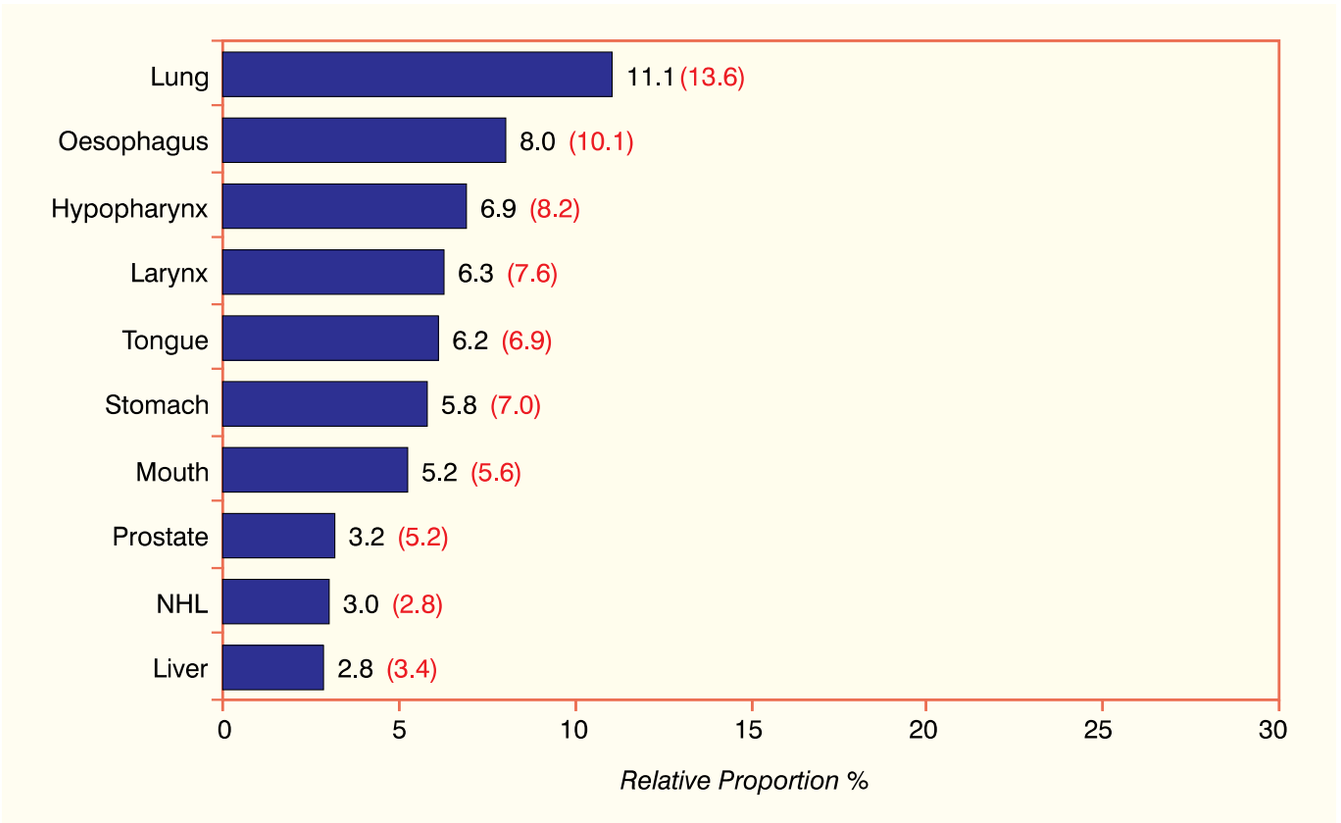


Fig. 3.6(a): Ten Leading Sites of Cancer – Males : Mumbai

Age Adjusted Incidence Rates given in parentheses

1982-1983



2004-2005

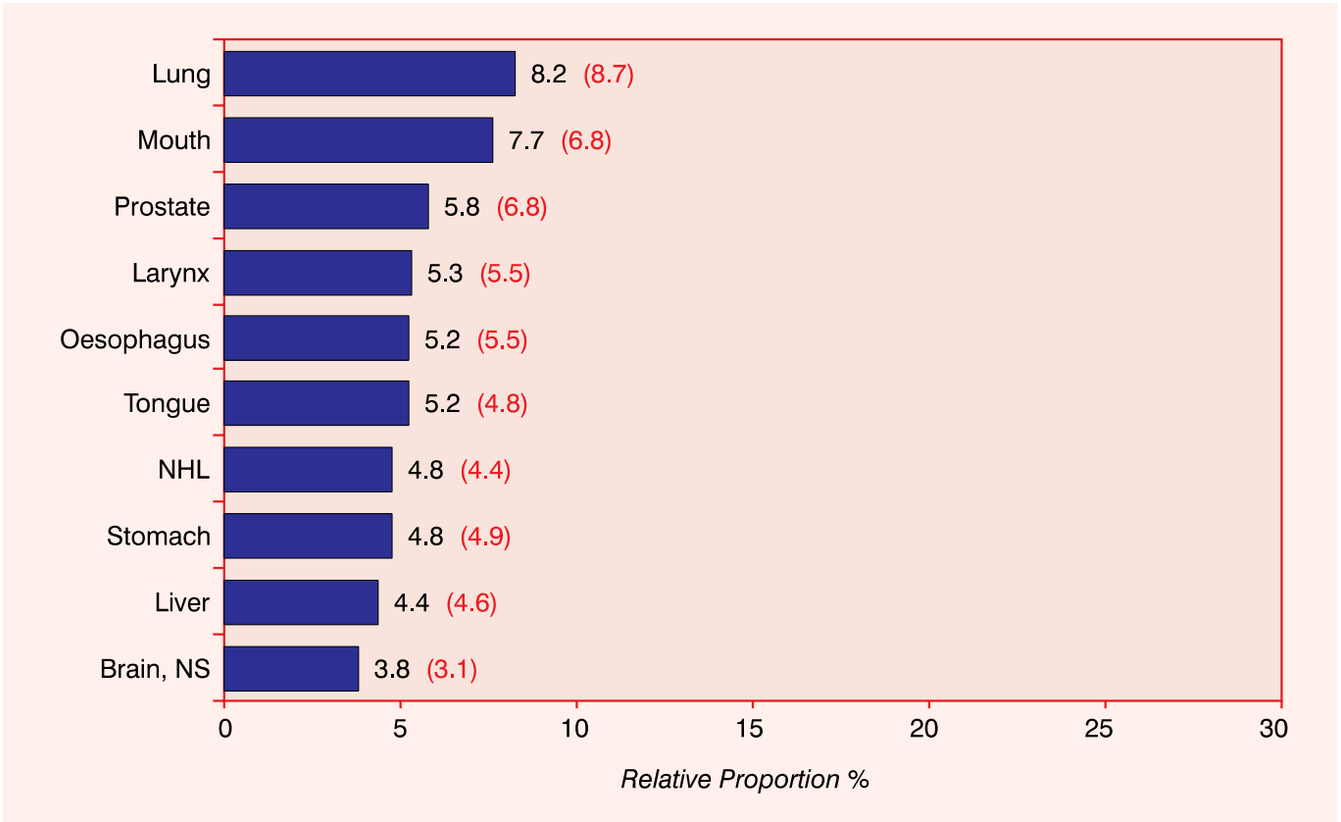
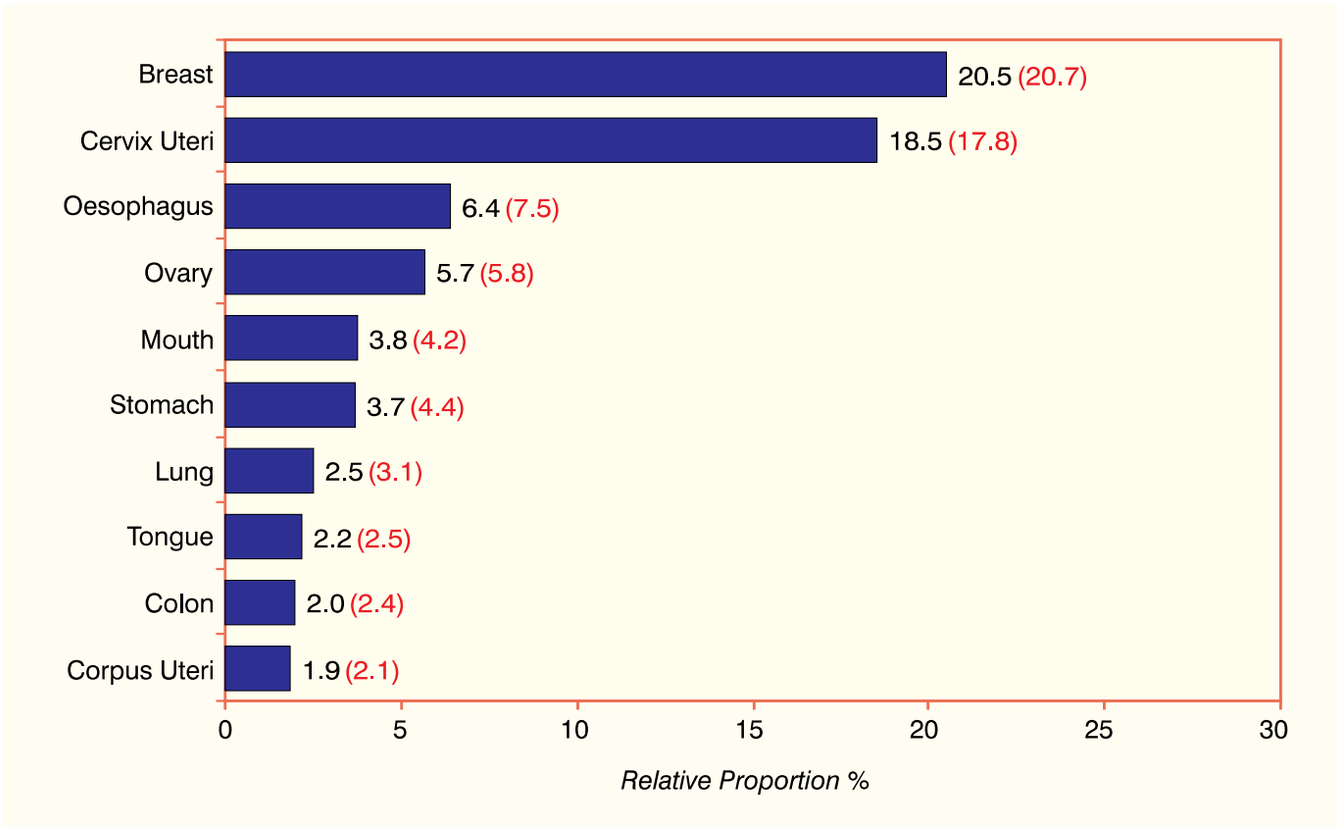


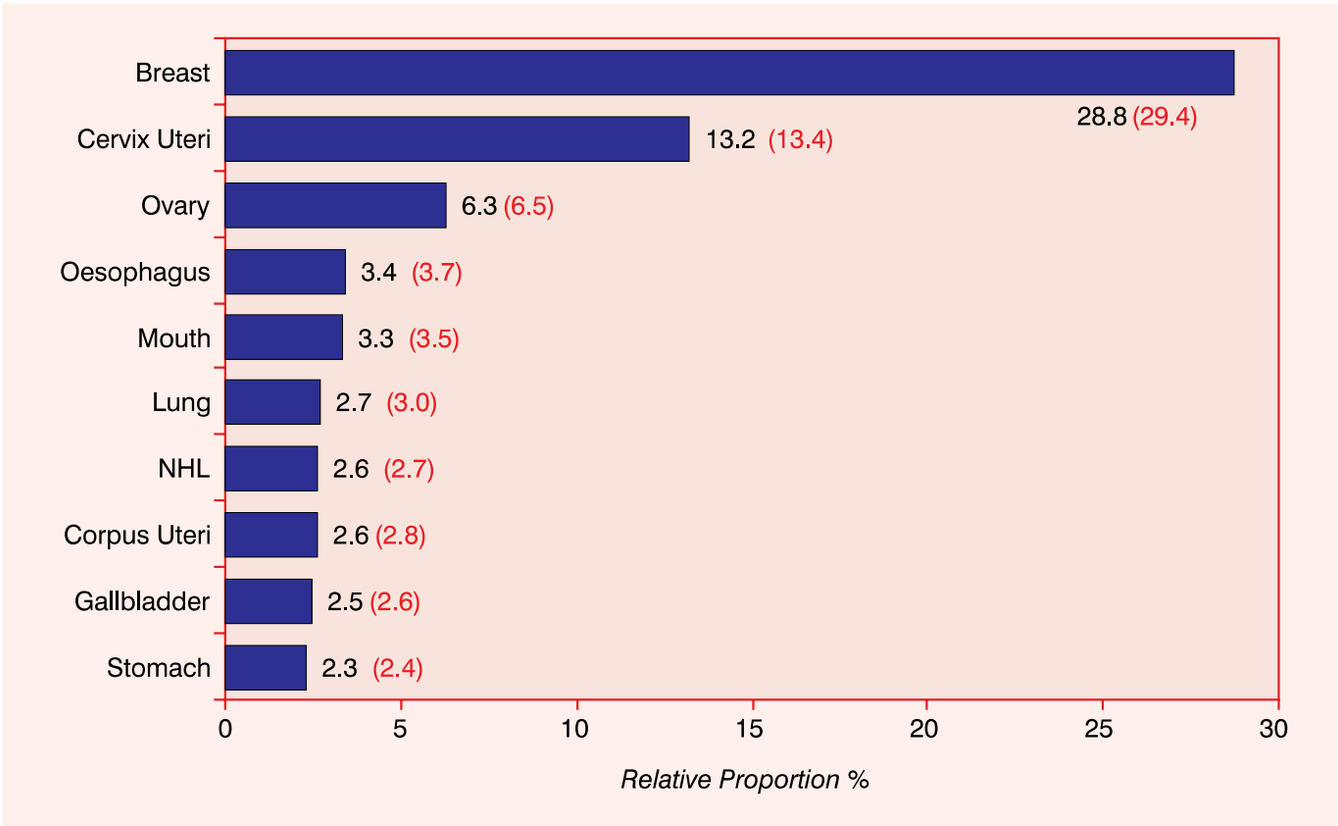
Fig. 3.6(b): Ten Leading Sites of Cancer – Females : Mumbai

Age Adjusted Incidence Rates given in parentheses

1982-1983



2004-2005



Chapter 4

TRENDS OVER TIME FOR ALL SITES AND ON SELECTED LEADING SITES OF CANCER

As mentioned in Chapter 2 the following sites have been included / excluded for the Barshi and Bhopal registries. In principle, anatomical sites with small numbers (less than ten cases per year) have been excluded.

For Barshi registry, only the following have been included:

(a) All anatomical sites (combined) in both males and females.
(b) Cancer of the breast and cervix in females.

All other sites have been excluded due to small numbers.

The following anatomical sites were excluded for Bhopal PBCR on account of small numbers. For males, the sites excluded were stomach, colon, rectum, liver, lymphoid and myeloid leukaemia. For females, the sites excluded were lung, corpus uteri, brain, NHL, thyroid gland and myeloid leukaemia. Certain other sites in Bhopal PBCR such as mouth in females, oesophagus in both males & females and Brain-NS in males have numbers in the teens and included. This needs to be kept in mind while interpreting the results.

Besides, in general, the ten leading sites of cancer across all registries have been chosen to depict trends over time.

Format of presentation for all sites and each of the selected anatomical sites :

The line graphs based on three year moving averages with the table below is shown on the left hand page. The facing page on the right shows Joinpoint Regression Model Trend lines with the corresponding table.

The table below the graph on three year Moving Average shows (i) the actual AAR values for each PBCR according to calendar year (ii) value of b (slope) and (iii) p-value with the values based on linear regression. In the facing page, the table below the Joinpoint Regression line gives the expected AAR values with respective Annual Percent Change (APC).

All Sites (Figure 4.1, 4.2 and Table 4.1, 4.2) :

Males: Both linear regression and joinpoint regression model did not show statistically significant increase or decrease in AAR over time in Bangalore, Barshi, Bhopal and Delhi PBCRs. Chennai PBCR showed a

significant rise in AAR over time. For the period 1982-1988, the APC was higher (4.5%) while from 1989–2005 this was 0.28%. Mumbai PBCR showed relative stable rates till 1990 with a decline thereafter.

Females: The PBCRs at Bangalore, Barshi, Bhopal and Chennai did not show a statistically significant change from 1982–2005. A statistically significant decline in AAR was observed for Delhi and Mumbai PBCR. For Mumbai PBCR, there was initial period of rise in AARs from 1982–1992, followed by a decline from 1993–2005.

Tongue (Figure 4.3 and Table 4.3) :

Males: There was no change in incidence rates trend over time for PBCRs of Bangalore, Bhopal and Delhi. Chennai showed an increasing trend whereas Mumbai showed a decline. The APC for Chennai was 1.3 and for Mumbai -2.0.

Mouth (Figure 4.4, 4.5 and Table 4.4, 4.5) :

Males: A rising trend was observed in both Delhi and Mumbai PBCR. The overall APC was 2.0 and 0.9 for Delhi and Mumbai respectively. The APC for Mumbai was higher (APC: 3.98) during later years (1998-2005).

Females: The registries at Bangalore, Delhi, Chennai and Mumbai showed a decline. The APC varied from -0.8 in Mumbai to -3.2 at Bangalore.

Hypopharynx (Figure 4.6 and Table 4.6) :

Males: The three PBCRs at Bangalore, Bhopal and Mumbai showed a decline in the AARs. The APC varied from -1.4 in Bangalore to -4.2 in Mumbai.

Oesophagus (Figure 4.7, 4.8 and Table 4.7, 4.8) :

Males: Only Delhi and Mumbai PBCRs showed a change in the AAR with a decline. The APC was -1.3 in Delhi and -3.1 in Mumbai.

Females: Bangalore, Bhopal, Delhi and Mumbai showed a decline with the APC ranging from -1.2 in Bangalore to -3.5 in Mumbai.

Stomach (Figure 4.9 and Table 4.9) :

Males: The AARs were unchanged over time for Bangalore and Delhi, whereas a decline was seen in Chennai and Mumbai PBCRs. The APC was -0.9 for Chennai and -2.2 for Mumbai. The decrease in Chennai was greater (APC: -1.5) for the later years (1987-2005).

Colon (Figure 4.10 and Table 4.10) :

Males: The PBCRs at Bangalore, Chennai and Delhi showed a statistically significant increase in the incidence of colon cancer. The APC was 1.7 in Delhi and 2.2 at both Bangalore and Chennai PBCRs.

Rectum (Figure 4.11 and Table 4.11) :

Males: Both Bangalore and Chennai showed a statistically significant increase in incidence rate trends over time. The APC was 1.6 for Bangalore and 2.5 for Chennai.

Liver (Figure 4.12 and Table 4.12) :

Males: The four PBCRs at Bangalore, Chennai, Delhi and Mumbai showed a statistically significant increase in the incidence of this cancer. The APC varied from 1.6 in Chennai to 2.0 in Bangalore. In Mumbai the change was higher (APC: 2.6) for later years (1997-2005).

Gallbladder (Figure 4.13 and Table 4.13) :

Females: The PBCRs at Bangalore, Bhopal, Chennai and Mumbai showed a statistically significant increase in the incidence of gallbladder cancer. The APC varied from 2.5 in Mumbai to 5.9 in Bangalore and Chennai. In Delhi PBCR a 15% increase was observed annually from 1988–1993, but thereafter a significant decline was observed. In Mumbai the change (APC: 9.1) was more during the earlier years (1982-1991).

Larynx (Figure 4.14 and Table 4.14) :

Males: Bhopal PBCR showed a significant increase whereas Mumbai PBCR showed a significant decrease in incidence rates over the years. The APC for Bhopal was 2.9 and -1.5 for Mumbai.

Lung (Figure 4.15, 4.16 and Table 4.15, 4.16) :

Males: Chennai and Delhi PBCRs showed a statistically significant increase in AARs of lung cancer with APC being 2.3 in Chennai and 1.0 in Delhi. In Chennai the change was higher (APC: 8.2) during the years 1982-1990.

Females: The three PBCRs at Bangalore, Chennai and Delhi showed an increase in the incidence of lung cancer over time with the APC varying from 2.0 in Delhi to 4.6 in Chennai.

Breast – Females (Figure 4.17 and Table 4.17) :

All the urban registries at Bangalore, Bhopal, Chennai, Delhi and Mumbai showed statistically significant increase in the incidence of breast cancer. The APC varied from 1.0 in Delhi to 2.7 in Bangalore. In Chennai the increase was more (APC: 4.0) during the later years (1995-2005) while in Mumbai the increase was more (APC: 3.1) during earlier years (1982-1991).

Cervix (Figure 4.18 and Table 4.18) :

All the six PBCRs have recorded a statistically significant decline in the incidence rates of cancer cervix. This includes the rural registry at Barshi. The APC varied from -1.4 in Bhopal to -3.4 in Delhi.

Corpus Uteri (Figure 4.19 and Table 4.19) :

The four registries at Bangalore, Chennai, Delhi and Mumbai showed a statistically significant increase in the incidence of cancer of corpus uteri. The APC varied from 1.7 in Mumbai to 5.8 in Bangalore.

Ovary – Females (Figure 4.20 and Table 4.20) :

Bangalore and Mumbai PBCRs showed an increase in the occurrence of incidence rates of this cancer. The APC was 0.8 in Mumbai and 1.7 in Bangalore. The increase in Mumbai was more (APC: 2.64) during earlier years.

Prostate (Figure 4.21 and Table 4.21) :

The four registries at Bangalore, Chennai, Delhi and Mumbai showed a statistically significant increase in the incidence of prostate cancer with the APC varying from 0.8 in Mumbai to 4.7 in Chennai.

Brain (Figure 4.22, 4.23 and Table 4.22, 4.23) :

Males: The PBCRs at Bangalore, Chennai and Mumbai showed an increase in the AARs. The APC was 2.7 in Mumbai PBCR, 3.0 in Chennai PBCR and 3.2 in Bangalore PBCR.

Females: As in males, Bangalore, Chennai and Mumbai showed a statistically significant increase in the occurrence of this cancer. The APC was 2.9 in Mumbai and 3.4 in Bangalore and 4.6 in Chennai.

Thyroid Gland (Figure 4.24 and Table 4.24) :

Females: Chennai and Delhi PBCR recorded an increase with the APC being 2.2 in Delhi and 2.6 in Chennai. The increase in Chennai was more (APC: 8.23) during the years 1996-2005.

NHL (Figure 4.25, 4.26 and Table 4.25, 4.26) :

Males: All the five urban PBCRs showed a statistically significant increase in the incidence of NHL. The APC varied from 1.0 in Delhi to 7.9 in Bhopal.

Females: Bangalore, Chennai, Delhi and Mumbai PBCRs showed as in males, a statistically significant increase in the incidence of this cancer. The APC varied from 1.2 in Delhi to 3.6 in Bangalore. The increase in both Chennai (APC: 5.1) and Mumbai (APC: 4.1) was more during the early years (1982-97).

Lymphoid Leukaemia (Figure 4.27 and Table 4.27) :

Males: Bangalore and Chennai PBCRs recorded an increase in the incidence of this cancer with the APC being 2.6 in Chennai and 2.7 in Bangalore.

Myeloid Leukaemia (Figure 4.28, 4.29 and Table 4.28, 4.29) :

Males: PBCRs at Bangalore, Chennai and Mumbai showed an increase in AARs with the APC being 0.8 in Mumbai to 2.2 in Bangalore and 2.5 in Chennai.

Females: As in males, both Bangalore and Chennai showed an increase in incidence rates with the APC being 1.9 in Bangalore and 3.4 in Chennai.

Lung cancer in Chennai women increased annually at the rate of 4.6%.

Both Chennai and Bangalore recorded an APC of 5.8% increase annually in the incidence of gallbladder cancer.

Cancer of the breast increased at the rate of 4% annually in Chennai females from 1995 to 2005. Likewise Chennai females also recorded an annual percentage increase of 8.2 for Thyroid cancers during 1995-2005.

Fig. 4.1(a): ALL SITES (ICD-10 : C00-C96) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

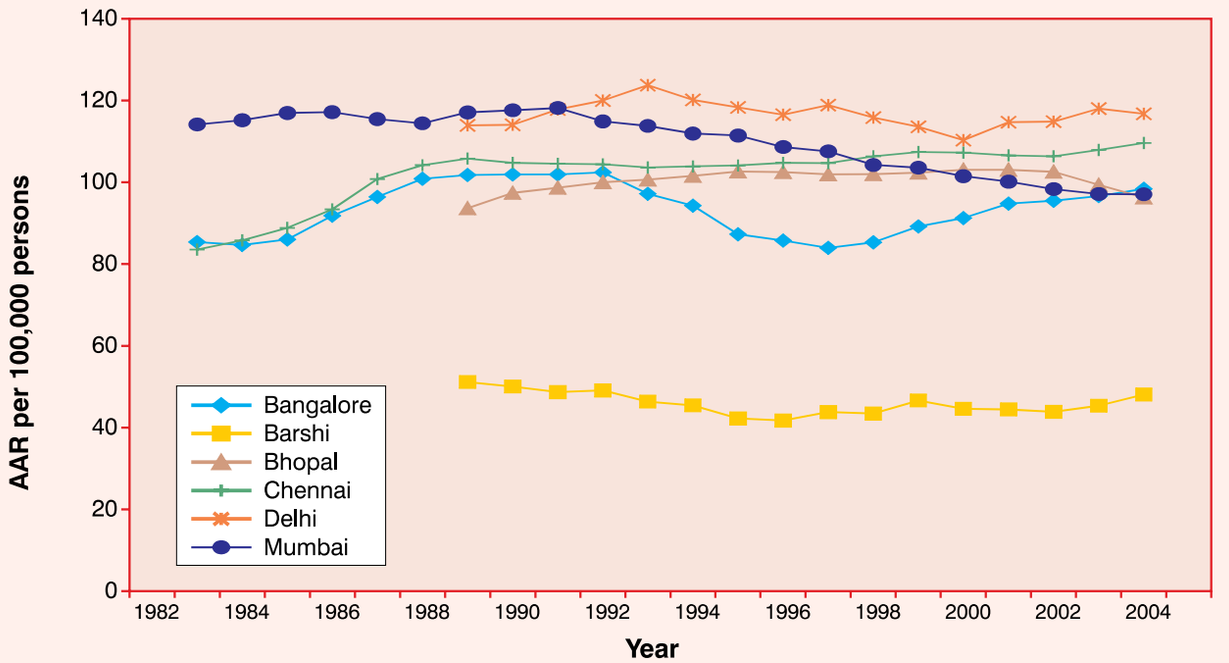


Table 4.1(a): Year wise AARs

Year	Bangalore	Barshi	Bhopal	Chennai	Delhi	Mumbai
1982	90.7			80.2		115.9
1983	83.5			85.9		110.9
1984	81.8			84.6		115.7
1985	88.7			87.0		119.0
1986	87.4			94.9		116.3
1987	99.3			98.3		116.2
1988	102.5	51.2	88.9	109.1	111.3	113.9
1989	100.8	51.4	95.9	105.2	112.5	113.1
1990	101.9	50.9	96.1	103.2	117.9	124.3
1991	103.0	47.8	100.3	105.9	111.8	115.2
1992	100.8	47.4	99.7	104.6	123.6	115.0
1993	103.4	52.1	100.0	102.6	124.5	114.5
1994	87.3	39.6	102.2	103.6	123.0	111.9
1995	92.2	44.7	102.4	105.5	112.9	109.4
1996	82.3	42.5	103.2	103.3	119.0	113.0
1997	82.7	38.2	101.8	105.4	117.8	103.6
1998	87.0	50.8	100.8	105.4	120.0	106.2
1999	86.1	41.4	103.4	108.3	109.8	103.0
2000	94.4	47.7	102.7	108.7	110.9	101.4
2001	93.3	44.7	103.0	104.8	110.3	100.1
2002	96.7	40.8	103.3	106.2	123.0	99.0
2003	96.5	46.0	101.4	108.2	111.3	95.8
2004	96.7	49.3	93.3	109.4	119.8	96.6
2005	102.0	49.1	94.1	111.3	119.2	98.6
Slope(b)	**0.169**	**-0.247**	**0.208**	**0.986**	**0.019**	**-0.961**
p-value	0.451	0.228	0.287	**0.001**	0.938	**0.001**

Fig. 4.1(b): ALL SITES (ICD-10 : C00-C96) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

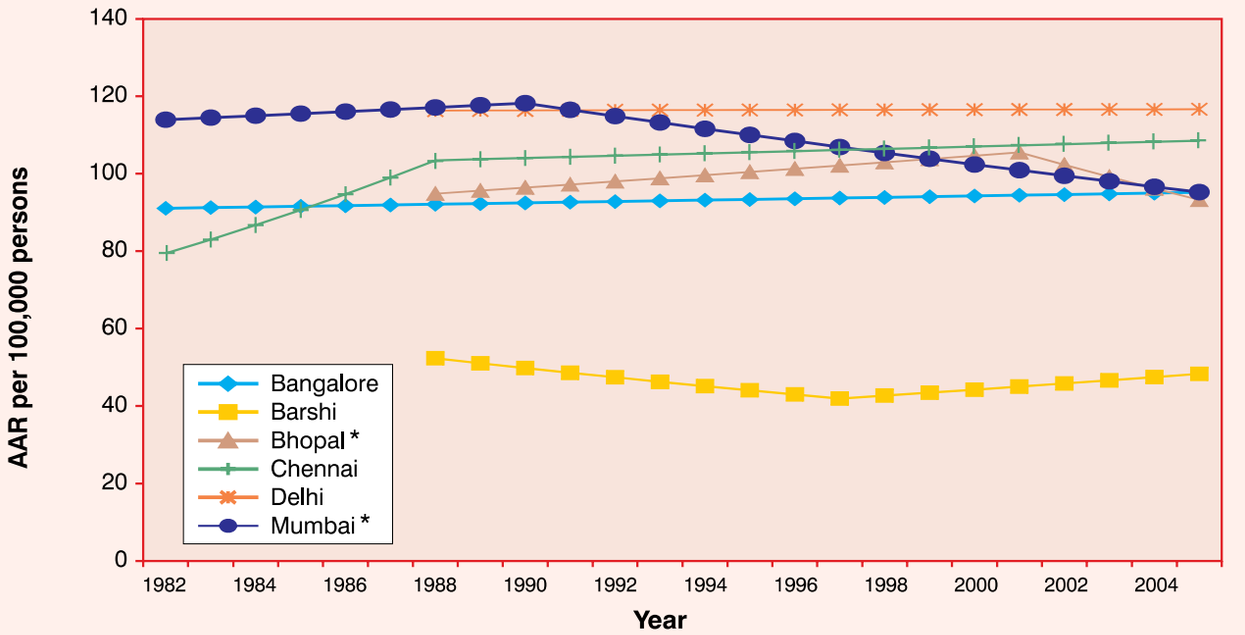


Table 4.1(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Barshi	Bhopal	Chennai	Delhi	Mumbai
	JP0*	**JP1***	**JP1***	**JP1***	**JP0***	**JP1***
1982	91.1			79.4		113.9
1983	91.2			83.0		114.5
1984	91.4			86.7		115.0
1985	91.6			90.6		115.5
1986	91.8			94.7		116.1
1987	91.9			99.0		116.6
1988	92.1	52.3	94.9	**103.4**	116.3	117.1
1989	92.3	51.1	95.6	103.7	116.3	117.7
1990	92.5	49.8	96.4	104.0	116.4	**118.2**
1991	92.7	48.6	97.2	104.3	116.4	116.5
1992	92.8	47.4	98.0	104.6	116.4	114.9
1993	93.0	46.3	98.8	104.9	116.4	113.2
1994	93.2	45.2	99.6	105.2	116.4	111.6
1995	93.4	44.1	100.4	105.5	116.5	110.0
1996	93.5	43.0	101.3	105.8	116.5	108.4
1997	93.7	**42.0**	102.1	106.1	116.5	106.9
1998	93.9	42.7	102.9	106.4	116.5	105.4
1999	94.1	43.5	103.8	106.7	116.5	103.8
2000	94.3	44.3	104.6	107.0	116.6	102.4
2001	94.4	45.0	**105.5**	107.3	116.6	100.9
2002	94.6	45.8	102.3	107.6	116.6	99.5
2003	94.8	46.7	99.2	107.9	116.6	98.0
2004	95.0	47.5	96.2	108.2	116.6	96.6
2005	95.2	48.3	93.3	108.5	116.7	95.3
APC0	0.19	-0.52	0.21	**1.03***	0.02	**-0.89***
APC1	–	**-2.42***	**0.82***	**4.50***	–	0.46
APC2	–	1.78	**-3.04***	**0.28***	–	**-1.43***

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.2(a): ALL SITES (ICD-10 : C00-C96) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

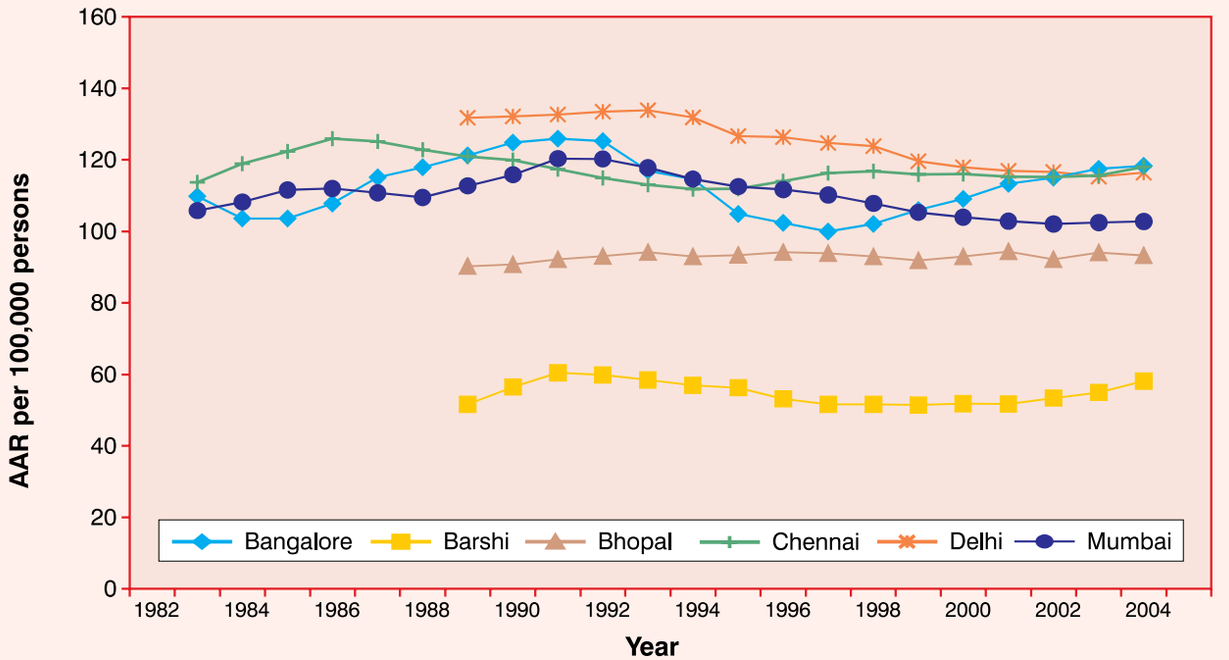


Table 4.2(a): Year wise AARs

Year	Bangalore	Barshi	Bhopal	Chennai	Delhi	Mumbai
1982	117.5			106.2		107.7
1983	105.8			118.6		101.8
1984	105.9			116.4		107.8
1985	98.9			121.9		115.0
1986	105.9			128.8		112.0
1987	118.4			127.1		109.0
1988	121.0	48.9	89.5	119.4	127.0	111.2
1989	114.2	49.7	90.1	121.8	133.1	108.4
1990	128.4	56.3	90.9	121.6	135.3	118.6
1991	131.9	63.3	91.3	116.4	128.0	120.6
1992	117.6	61.8	94.1	114.2	134.5	121.8
1993	126.3	54.4	93.6	114.0	137.7	118.1
1994	106.8	59.2	94.6	110.9	129.2	113.5
1995	110.8	57.4	90.6	110.6	128.7	112.0
1996	97.2	52.1	94.7	114.1	122.0	111.9
1997	99.3	50.0	97.2	117.3	128.4	111.2
1998	103.4	52.9	89.6	117.6	123.9	107.3
1999	103.5	51.9	92.0	115.5	119.1	104.7
2000	110.9	49.7	93.8	114.7	116.0	103.8
2001	112.9	54.0	93.1	117.9	118.7	103.3
2002	116.1	51.7	96.3	113.3	116.1	101.6
2003	116.1	54.5	87.2	114.5	114.9	101.2
2004	120.2	58.7	98.8	119.0	114.8	104.6
2005	118.6	61.2	93.7	120.4	119.4	102.4
Slope(b)	**0.049**	**0.037**	**0.192**	**-0.134**	**-1.190**	**-0.358**
p-value	0.865	0.861	0.161	0.378	**0.001**	**0.046**

Fig. 4.2(b): ALL SITES (ICD-10 : C00-C96) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

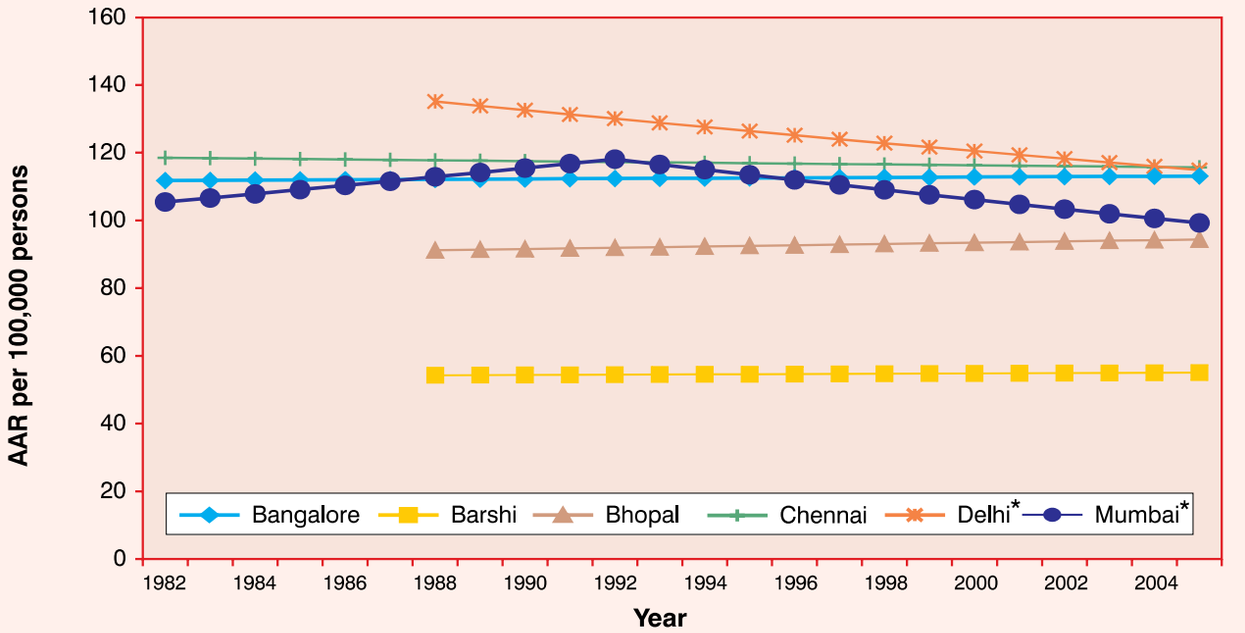


Table 4.2(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Barshi	Bhopal	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*	JP0*	JP1*
1982	111.8			118.5		105.4
1983	111.8			118.4		106.6
1984	111.9			118.2		107.9
1985	112.0			118.1		109.1
1986	112.0			118.0		110.3
1987	112.1			117.9		111.6
1988	112.1	54.3	91.2	117.7	135.2	112.9
1989	112.2	54.3	91.4	117.6	133.9	114.2
1990	112.2	54.4	91.6	117.5	132.6	115.5
1991	112.3	54.4	91.8	117.4	131.3	116.8
1992	112.4	54.5	92.0	117.2	130.1	**118.1**
1993	112.4	54.5	92.1	117.1	128.8	116.5
1994	112.5	54.6	92.3	117.0	127.6	115.0
1995	112.5	54.6	92.5	116.9	126.4	113.5
1996	112.6	54.7	92.7	116.8	125.2	112.0
1997	112.6	54.7	92.9	116.6	124.0	110.5
1998	112.7	54.8	93.1	116.5	122.8	109.0
1999	112.8	54.8	93.3	116.4	121.7	107.6
2000	112.8	54.9	93.5	116.3	120.5	106.1
2001	112.9	54.9	93.6	116.1	119.4	104.7
2002	112.9	55.0	93.8	116.0	118.2	103.4
2003	113.0	55.0	94.0	115.9	117.1	102.0
2004	113.0	55.1	94.2	115.8	116.0	100.6
2005	113.1	55.1	94.4	115.7	114.9	99.3
APC0	0.05	0.09	0.20	-0.10	**-0.95***	**-0.33***
APC1	–	–	–	–	–	**1.14***
APC2	–	–	–	–	–	**-1.33***

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.3(a): TONGUE (ICD-10 : C01-C02) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

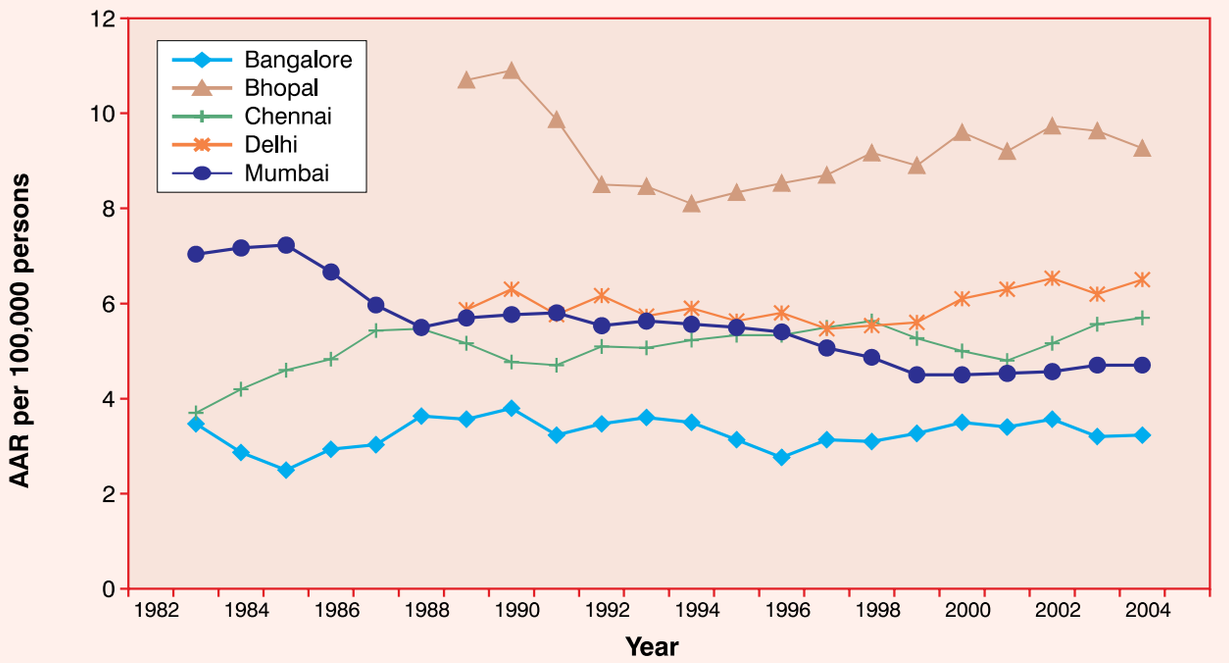


Table 4.3(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	4.1		3.7		6.9
1983	3.6		3.4		6.9
1984	2.7		4.0		7.3
1985	2.3		5.2		7.3
1986	2.5		4.6		7.1
1987	4.0		4.7		5.6
1988	2.6	8.1	7.0	4.9	5.2
1989	4.3	11.9	4.7	7.3	5.7
1990	3.8	12.1	3.8	5.4	6.2
1991	3.3	8.7	5.8	6.2	5.4
1992	2.6	8.8	4.5	5.7	5.8
1993	4.5	8.0	5.0	6.6	5.4
1994	3.7	8.6	5.7	4.9	5.7
1995	2.3	7.7	5.0	6.2	5.6
1996	3.4	8.7	5.3	5.8	5.2
1997	2.6	9.2	5.7	5.4	5.4
1998	3.4	8.2	5.5	5.2	4.6
1999	3.3	10.1	5.7	6.0	4.6
2000	3.1	8.4	4.6	5.6	4.3
2001	4.1	10.3	4.7	6.7	4.6
2002	3.0	8.9	5.1	6.6	4.7
2003	3.6	10.0	5.7	6.3	4.4
2004	3.0	10.0	5.9	5.7	5.0
2005	3.1	7.8	5.5	7.5	4.7
Slope(b)	**0.001**	**-0.035**	**0.056**	**0.043**	**-0.116**
p-value	0.988	0.567	0.018	0.218	**0.001**

Fig. 4.3(b): TONGUE (ICD-10 : C01-C02) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

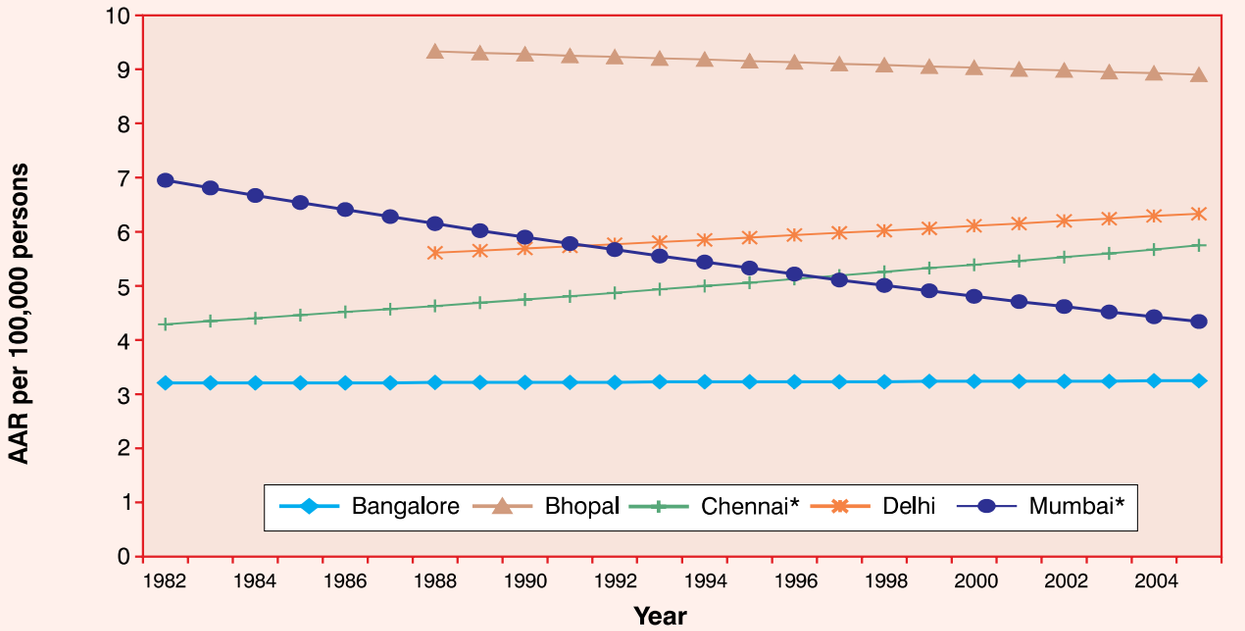


Table 4.3(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*	JP0*
1982	3.2		4.3		7.0
1983	3.2		4.4		6.8
1984	3.2		4.4		6.7
1985	3.2		4.5		6.5
1986	3.2		4.5		6.4
1987	3.2		4.6		6.3
1988	3.2	9.3	4.6	5.6	6.2
1989	3.2	9.3	4.7	5.7	6.0
1990	3.2	9.3	4.8	5.7	5.9
1991	3.2	9.3	4.8	5.7	5.8
1992	3.2	9.2	4.9	5.8	5.7
1993	3.2	9.2	4.9	5.8	5.6
1994	3.2	9.2	5.0	5.9	5.4
1995	3.2	9.2	5.1	5.9	5.3
1996	3.2	9.1	5.1	5.9	5.2
1997	3.2	9.1	5.2	6.0	5.1
1998	3.2	9.1	5.3	6.0	5.0
1999	3.2	9.1	5.3	6.1	4.9
2000	3.2	9.0	5.4	6.1	4.8
2001	3.2	9.0	5.5	6.2	4.7
2002	3.2	9.0	5.5	6.2	4.6
2003	3.2	9.0	5.6	6.2	4.5
2004	3.3	8.9	5.7	6.3	4.4
2005	3.3	8.9	5.8	6.3	4.3
APC0	0.06	-0.28	**1.27***	0.72	**-2.03***
APC1	–	–	–	–	–
APC2	–	–	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.4(a): MOUTH (ICD-10 : C03-C06) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

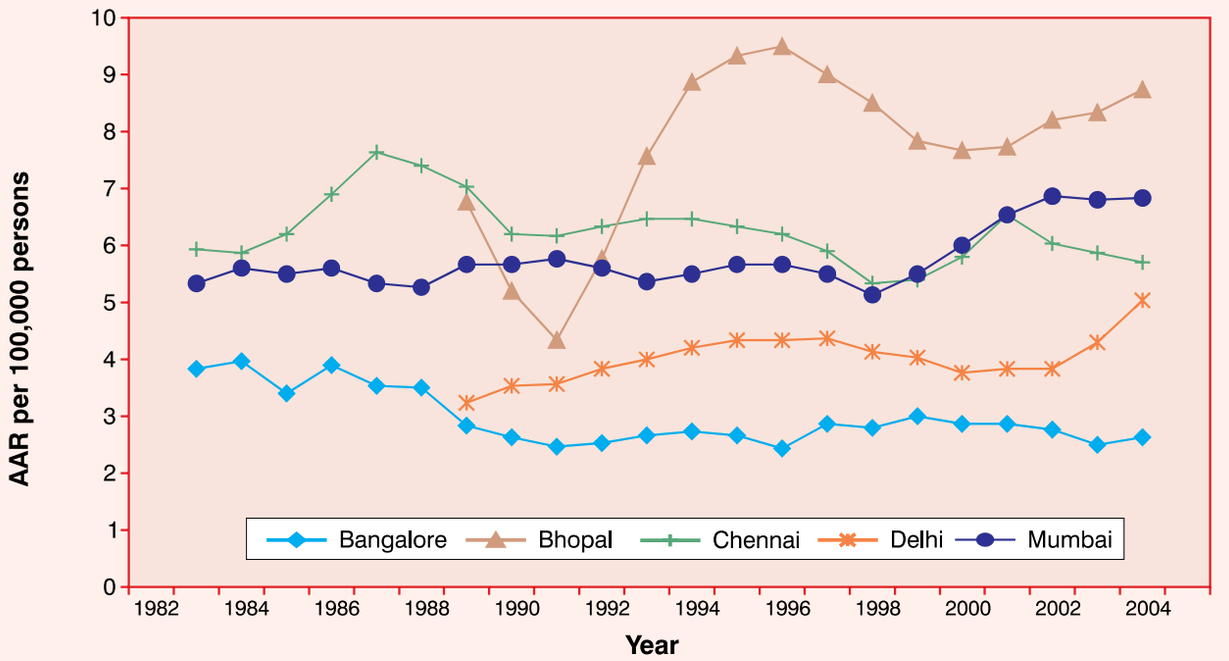


Table 4.4(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	3.7		6.4		5.6
1983	4.5		6.0		5.7
1984	3.3		5.4		4.7
1985	4.1		6.2		6.4
1986	2.8		7.0		5.4
1987	4.8		7.5		5.0
1988	3.0	8.0	8.4	3.0	5.6
1989	2.7	9.1	6.3	3.5	5.2
1990	2.8	3.2	6.4	3.2	6.2
1991	2.4	3.3	5.9	3.9	5.6
1992	2.2	6.5	6.2	3.6	5.5
1993	3.0	7.5	6.9	4.0	5.7
1994	2.8	8.7	6.3	4.4	4.9
1995	2.4	10.4	6.2	4.2	5.9
1996	2.8	8.9	6.5	4.4	6.2
1997	2.1	9.2	5.9	4.4	4.9
1998	3.7	8.9	5.3	4.3	5.4
1999	2.6	7.4	4.8	3.7	5.1
2000	2.7	7.2	6.1	4.1	6.0
2001	3.3	8.4	6.5	3.5	6.9
2002	2.6	7.6	7.0	3.9	6.7
2003	2.4	8.6	4.6	4.1	7.0
2004	2.5	8.8	6.0	4.9	6.7
2005	3.0	8.8	6.5	6.1	6.8
Slope(b)	**-0.052**	**0.135**	**-0.032**	**0.085**	**0.054**
p-value	**0.008**	0.118	0.175	**0.003**	**0.005**

Fig. 4.4(b): MOUTH (ICD-10 : C03-C06) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

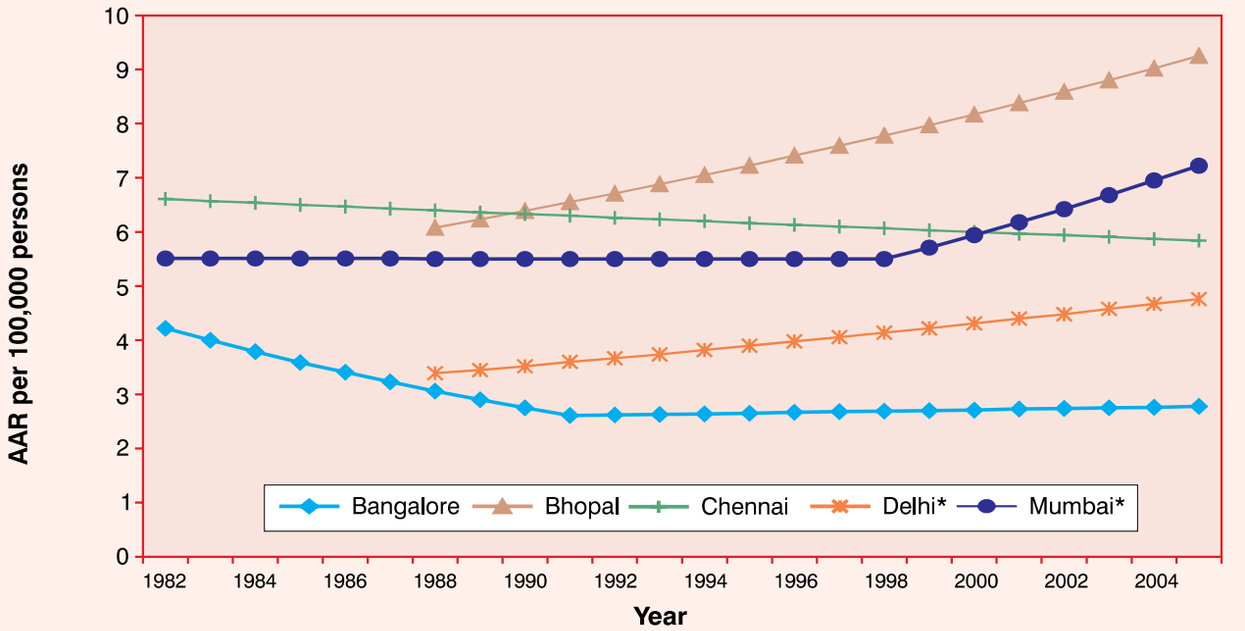


Table 4.4(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP1*	**JP0***	**JP0***	**JP0***	**JP1***
1982	4.2		6.6		5.5
1983	4.0		6.6		5.5
1984	3.8		6.5		5.5
1985	3.6		6.5		5.5
1986	3.4		6.5		5.5
1987	3.2		6.4		5.5
1988	3.1	6.1	6.4	3.4	5.5
1989	2.9	6.2	6.4	3.5	5.5
1990	2.8	6.4	6.3	3.5	5.5
1991	**2.6**	6.6	6.3	3.6	5.5
1992	2.6	6.7	6.3	3.7	5.5
1993	2.6	6.9	6.2	3.7	5.5
1994	2.6	7.1	6.2	3.8	5.5
1995	2.7	7.2	6.2	3.9	5.5
1996	2.7	7.4	6.1	4.0	5.5
1997	2.7	7.6	6.1	4.1	5.5
1998	2.7	7.8	6.1	4.1	**5.5**
1999	2.7	8.0	6.0	4.2	5.7
2000	2.7	8.2	6.0	4.3	5.9
2001	2.7	8.4	6.0	4.4	6.2
2002	2.7	8.6	5.9	4.5	6.4
2003	2.8	8.8	5.9	4.6	6.7
2004	2.8	9.0	5.9	4.7	7.0
2005	2.8	9.3	5.8	4.8	7.2
APC0	**-1.54***	2.5	-0.53	**2.03***	**0.89***
APC1	**-5.21***	–	–	–	-0.02
APC2	0.45	–	–	–	**3.98***

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.5(a): MOUTH (ICD-10 : C03-C06) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

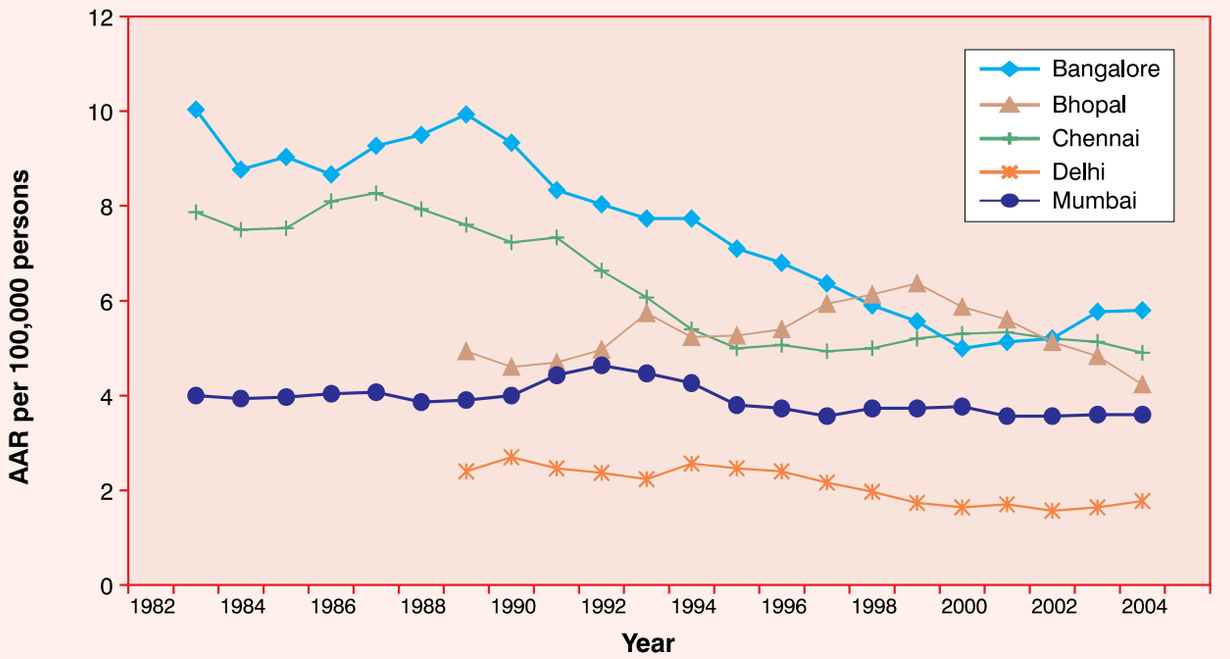


Table 4.5(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	12.2		8.4		4.3
1983	8.7		8.1		4.0
1984	9.2		7.1		3.7
1985	8.4		7.3		4.1
1986	9.5		8.2		4.1
1987	8.1		8.8		3.9
1988	10.2	4.3	7.8	2.2	4.2
1989	10.2	6.0	7.2	2.3	3.5
1990	9.4	4.5	7.8	2.7	4.0
1991	8.4	3.3	6.7	3.1	4.5
1992	7.2	6.3	7.5	1.6	4.8
1993	8.5	5.3	5.7	2.4	4.6
1994	7.5	5.6	5.0	2.7	4.0
1995	7.2	4.8	5.5	2.6	4.2
1996	6.6	5.4	4.5	2.1	3.2
1997	6.6	6.0	5.2	2.5	3.8
1998	5.9	6.4	5.1	1.9	3.7
1999	5.2	6.0	4.7	1.5	3.7
2000	5.6	6.7	5.8	1.8	3.8
2001	4.2	4.9	5.4	1.6	3.8
2002	5.6	5.2	4.8	1.7	3.1
2003	5.8	5.3	5.4	1.4	3.8
2004	5.9	4.0	5.2	1.8	3.9
2005	5.7	3.4	4.1	2.1	3.1
Slope(b)	**-0.242**	**-0.008**	**-0.176**	**-0.056**	**-0.028**
p-value	**0.001**	0.87	**0.001**	**0.006**	**0.022**

Fig. 4.5(b): MOUTH (ICD-10 : C03-C06) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

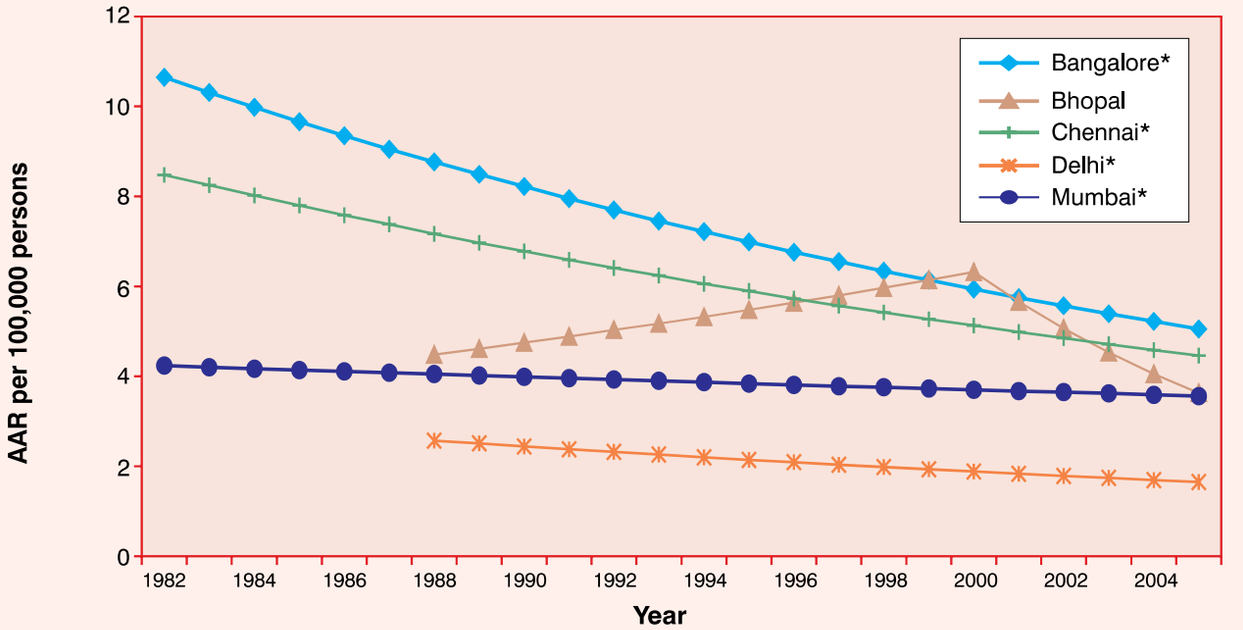


Table 4.5(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	**JP1***	**JP0***	**JP0***	**JP0***
1982	10.7		8.5		4.2
1983	10.3		8.3		4.2
1984	10.0		8.0		4.2
1985	9.7		7.8		4.1
1986	9.4		7.6		4.1
1987	9.1		7.4		4.1
1988	8.8	4.5	7.2	2.6	4.1
1989	8.5	4.6	7.0	2.5	4.0
1990	8.2	4.8	6.8	2.4	4.0
1991	8.0	4.9	6.6	2.4	4.0
1992	7.7	5.0	6.4	2.3	3.9
1993	7.5	5.2	6.2	2.3	3.9
1994	7.2	5.3	6.1	2.2	3.9
1995	7.0	5.5	5.9	2.1	3.8
1996	6.8	5.6	5.7	2.1	3.8
1997	6.6	5.8	5.6	2.0	3.8
1998	6.3	6.0	5.4	2.0	3.8
1999	6.1	6.1	5.3	1.9	3.7
2000	5.9	**6.3**	5.1	1.9	3.7
2001	5.8	5.7	5.0	1.8	3.7
2002	5.6	5.1	4.9	1.8	3.7
2003	5.4	4.5	4.7	1.7	3.6
2004	5.2	4.1	4.6	1.7	3.6
2005	5.1	3.6	4.5	1.7	3.6
APC0	**-3.19***	-0.23	**-2.76***	**-2.58***	**-0.75***
APC1	–	2.91	–	–	–
APC2	–	-10.51	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.6(a): HYPOPHARYNX (ICD-10 : C12-C13) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

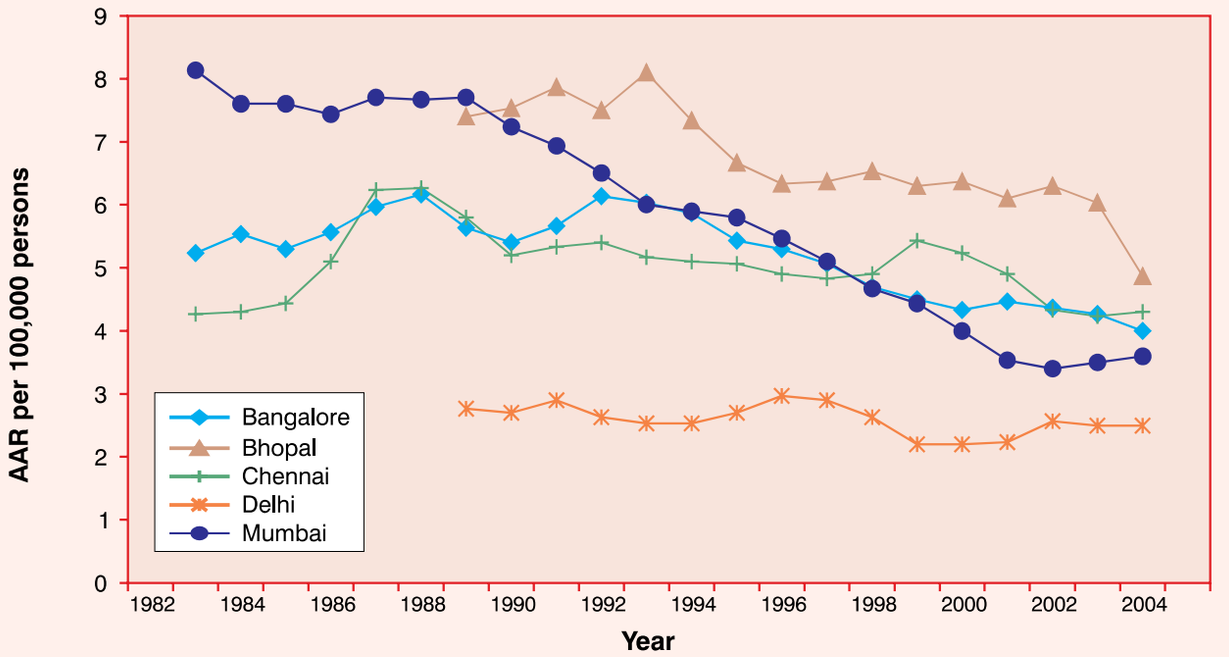


Table 4.6(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	4.4		3.5		9.1
1983	5.4		5.2		7.3
1984	5.9		4.1		8.0
1985	5.3		3.6		7.5
1986	4.7		5.6		7.3
1987	6.7		6.1		7.5
1988	6.5	5.2	7.0	2.9	8.3
1989	5.3	7.6	5.7	2.1	7.2
1990	5.1	9.4	4.7	3.3	7.6
1991	5.8	5.6	5.2	2.7	6.9
1992	6.1	8.6	6.1	2.7	6.3
1993	6.5	8.3	4.9	2.5	6.3
1994	5.5	7.4	4.5	2.4	5.4
1995	5.6	6.3	5.9	2.7	6.0
1996	5.2	6.3	4.8	3.0	6.0
1997	5.1	6.4	4.0	3.2	4.4
1998	4.9	6.4	5.7	2.5	4.9
1999	4.1	6.8	5.0	2.2	4.7
2000	4.5	5.7	5.6	1.9	3.7
2001	4.4	6.6	5.1	2.5	3.6
2002	4.5	6.0	4.0	2.3	3.3
2003	4.2	6.3	3.9	2.9	3.3
2004	4.1	5.8	4.8	2.3	3.9
2005	3.7	2.5	4.2	2.3	3.6
Slope(b)	**-0.068**	**-0.152**	**-0.015**	**-0.024**	**-0.240**
p-value	**0.003**	**0.020**	0.586	0.177	**0.001**

Fig. 4.6(b): HYPOPHARYNX (ICD-10 : C12-C13) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

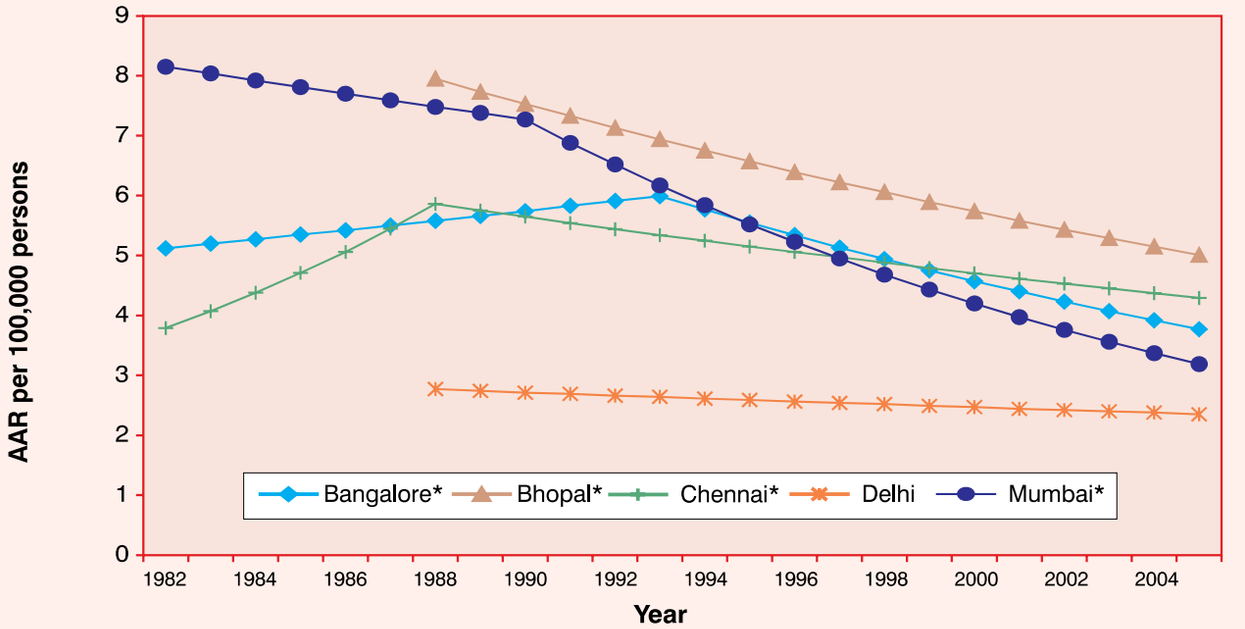


Table 4.6(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP1*	**JP0***	**JP1***	**JP0***	**JP1***
1982	5.1		3.8		8.2
1983	5.2		4.1		8.0
1984	5.3		4.4		7.9
1985	5.4		4.7		7.8
1986	5.4		5.1		7.7
1987	5.5		5.5		7.6
1988	5.6	8.0	**5.9**	2.8	7.5
1989	5.7	7.7	5.8	2.7	7.4
1990	5.7	7.5	5.7	2.7	**7.3**
1991	5.8	7.3	5.5	2.7	6.9
1992	5.9	7.1	5.4	2.7	6.5
1993	**6.0**	6.9	5.3	2.6	6.2
1994	5.8	6.8	5.3	2.6	5.8
1995	5.6	6.6	5.2	2.6	5.5
1996	5.3	6.4	5.1	2.6	5.2
1997	5.1	6.2	5.0	2.5	5.0
1998	4.9	6.1	4.9	2.5	4.7
1999	4.8	5.9	4.8	2.5	4.4
2000	4.6	5.7	4.7	2.5	4.2
2001	4.4	5.6	4.6	2.4	4.0
2002	4.2	5.4	4.5	2.4	3.8
2003	4.1	5.3	4.5	2.4	3.6
2004	3.9	5.2	4.4	2.4	3.4
2005	3.8	5.0	4.3	2.4	3.2
APC0	**-1.38***	**-2.68***	-0.20	-0.95	**-4.24***
APC1	1.44	–	7.55	–	-1.41
APC2	**-3.80***	–	**-1.82***	–	**-5.35***

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.7(a): OESOPHAGUS (ICD-10 : C15) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

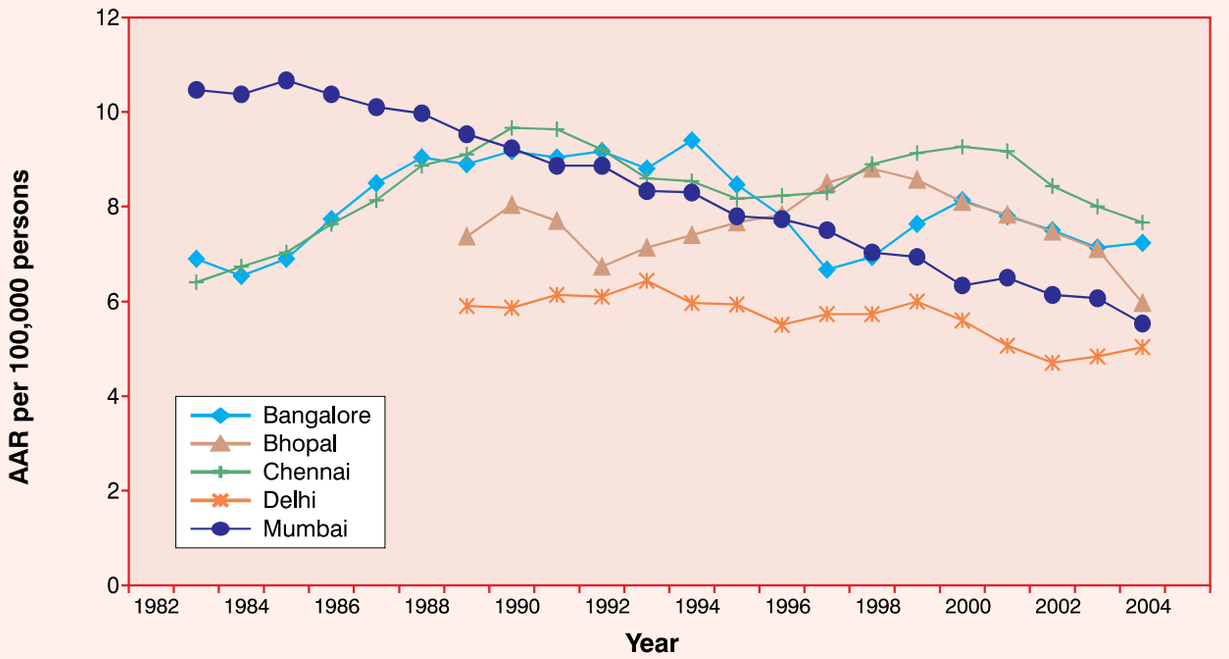


Table 4.7(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	7.6		6.2		10.9
1983	5.7		5.8		9.3
1984	7.4		7.2		11.2
1985	6.5		7.2		10.6
1986	6.8		6.7		10.2
1987	9.9		9.0		10.3
1988	8.8	5.2	8.7	5.5	9.8
1989	8.4	7.0	8.9	6.0	9.8
1990	9.5	9.9	9.7	6.2	9.0
1991	9.6	7.2	10.4	5.4	8.9
1992	8.0	6.0	8.8	6.8	8.7
1993	9.9	7.0	8.4	6.1	9.0
1994	8.5	8.4	8.6	6.4	7.3
1995	9.8	6.8	8.6	5.4	8.6
1996	7.1	7.8	7.3	6.0	7.5
1997	6.5	8.9	8.8	5.1	7.1
1998	6.4	8.8	8.8	6.1	7.9
1999	7.9	8.7	9.1	6.0	6.1
2000	8.6	8.2	9.5	5.9	6.8
2001	7.9	7.4	9.2	4.9	6.1
2002	6.9	7.9	8.8	4.4	6.6
2003	7.7	7.1	7.3	4.8	5.7
2004	6.8	6.3	7.9	5.3	5.9
2005	7.2	4.5	7.8	5.0	5.0
Slope(b)	**-0.014**	**-0.021**	**0.060**	**-0.070**	**-0.246**
p-value	0.718	0.740	0.068	**0.011**	**0.001**

Fig. 4.7(b): OESOPHAGUS (ICD-10 : C15) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

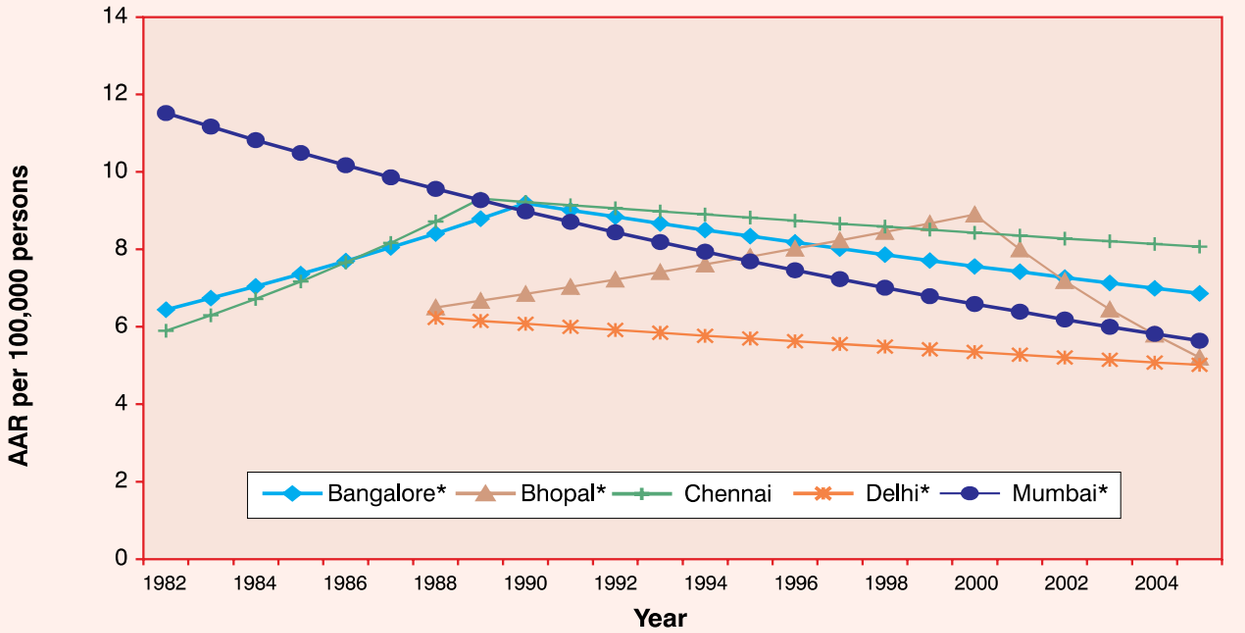


Table 4.7(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP1*	**JP1***	**JP1***	**JP0***	**JP0***
1982	6.4		5.9		11.5
1983	6.7		6.3		11.2
1984	7.0		6.7		10.8
1985	7.4		7.2		10.5
1986	7.7		7.7		10.2
1987	8.1		8.2		9.9
1988	8.4	6.5	8.7	6.2	9.6
1989	8.8	6.7	**9.3**	6.2	9.3
1990	9.2	6.9	9.2	6.1	9.0
1991	9.0	7.0	9.1	6.0	8.7
1992	8.8	7.2	9.1	5.9	8.4
1993	8.7	7.4	9.0	5.9	8.2
1994	8.5	7.6	8.9	5.8	7.9
1995	8.3	7.8	8.8	5.7	7.7
1996	8.2	8.0	8.7	5.6	7.5
1997	8.0	8.2	8.7	5.6	7.2
1998	7.9	8.5	8.6	5.5	7.0
1999	7.7	8.7	8.5	5.4	6.8
2000	7.6	**8.9**	8.4	5.4	6.6
2001	7.4	8.0	8.4	5.3	6.4
2002	7.3	7.2	8.3	5.2	6.2
2003	7.1	6.5	8.2	5.2	6.0
2004	7.0	5.8	8.1	5.1	5.8
2005	6.9	5.2	8.1	5.0	5.6
APC0	-0.12	-0.34	0.82	**-1.27***	**-3.06***
APC1	**4.54***	2.66	**6.73***	–	–
APC2	**-1.93***	**-10.17***	-0.89	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.8(a): OESOPHAGUS (ICD-10 : C15) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

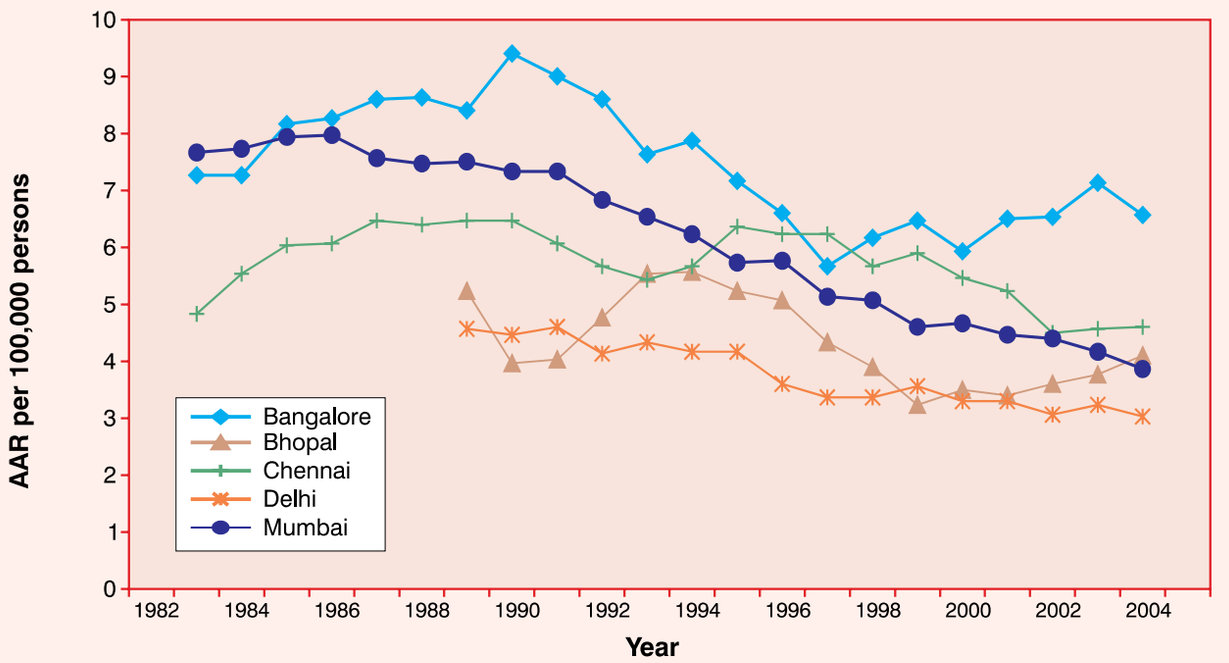


Table 4.8(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	6.5		3.2		8.1
1983	6.6		5.6		7.0
1984	8.7		5.7		7.9
1985	6.5		5.3		8.3
1986	9.3		7.1		7.6
1987	9.0		5.8		8.0
1988	7.5	7.2	6.5	4.3	7.1
1989	9.4	4.7	6.9	4.3	7.3
1990	8.3	3.8	6.0	5.1	8.1
1991	10.5	3.4	6.5	4.0	6.6
1992	8.2	4.9	5.7	4.7	7.3
1993	7.1	6.0	4.8	3.7	6.6
1994	7.6	5.7	5.8	4.6	5.7
1995	8.9	5.0	6.4	4.2	6.4
1996	5.0	5.0	6.9	3.7	5.1
1997	5.9	5.2	5.4	2.9	5.8
1998	6.1	2.8	6.4	3.5	4.5
1999	6.5	3.7	5.2	3.7	4.9
2000	6.8	3.2	6.1	3.5	4.4
2001	4.5	3.6	5.1	2.7	4.7
2002	8.2	3.4	4.5	3.7	4.3
2003	6.9	3.8	3.9	2.8	4.2
2004	6.3	4.1	5.3	3.2	4.0
2005	6.5	4.4	4.6	3.1	3.4
Slope(b)	**-0.084**	**-0.108**	**-0.029**	**-0.101**	**-0.021**
p-value	0.051	**0.029**	0.315	**0.001**	**0.001**

Fig. 4.8(b): OESOPHAGUS (ICD-10 : C15) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

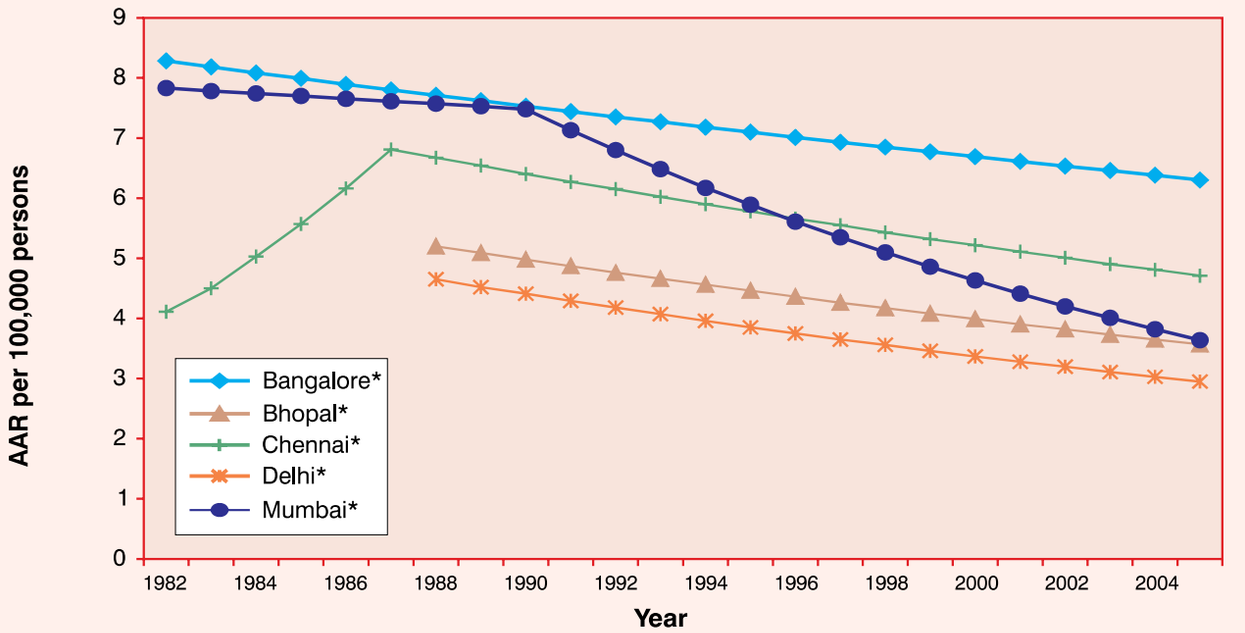


Table 4.8(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	**JP0***	**JP1***	**JP0***	**JP1***
1982	8.3		4.1		7.8
1983	8.2		4.5		7.8
1984	8.1		5.0		7.7
1985	8.0		5.6		7.7
1986	7.9		6.2		7.7
1987	7.8		**6.8**		7.6
1988	7.7	5.2	6.7	4.7	7.6
1989	7.6	5.1	6.5	4.5	7.5
1990	7.5	5.0	6.4	4.4	**7.5**
1991	7.4	4.9	6.3	4.3	7.1
1992	7.4	4.8	6.2	4.2	6.8
1993	7.3	4.7	6.0	4.1	6.5
1994	7.2	4.6	5.9	4.0	6.2
1995	7.1	4.5	5.8	3.9	5.9
1996	7.0	4.4	5.7	3.8	5.6
1997	6.9	4.3	5.6	3.7	5.4
1998	6.9	4.2	5.4	3.6	5.1
1999	6.8	4.1	5.3	3.5	4.9
2000	6.7	4.0	5.2	3.4	4.6
2001	6.6	3.9	5.1	3.3	4.4
2002	6.5	3.8	5.0	3.2	4.2
2003	6.5	3.7	4.9	3.1	4.0
2004	6.4	3.7	4.8	3.0	3.8
2005	6.3	3.6	4.7	3.0	3.6
APC0	**-1.18***	**-2.19***	-0.44	**-2.64***	**-3.52***
APC1	–	–	**10.63***	–	-0.56
APC2	–	–	**-2.03***	**–**	**-4.69***

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.9(a): STOMACH (ICD-10 : C16) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

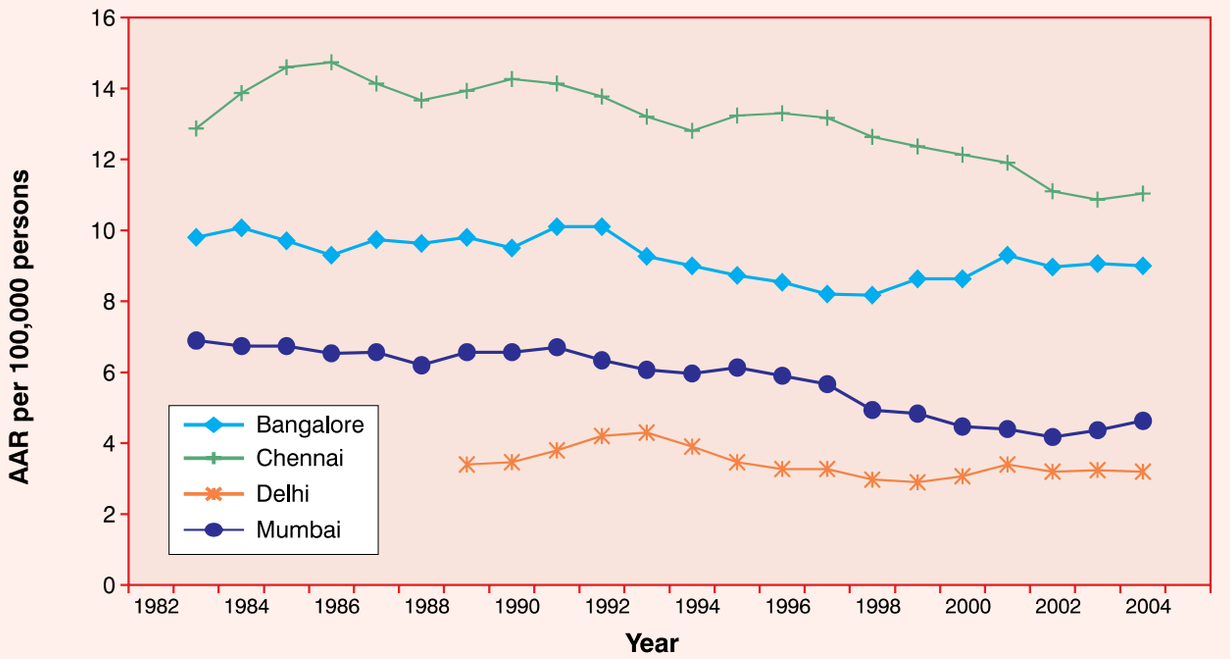


Table 4.9(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	10.0	11.8		7.1
1983	9.9	13.7		7.0
1984	9.5	13.1		6.6
1985	10.8	14.8		6.6
1986	8.8	15.9		7.0
1987	8.3	13.5		6.0
1988	12.1	13.0	3.4	6.7
1989	8.5	14.5	3.2	5.9
1990	8.8	14.3	3.6	7.1
1991	11.2	14.0	3.6	6.7
1992	10.3	14.1	4.2	6.3
1993	8.8	13.2	4.8	6.0
1994	8.7	12.3	3.9	5.9
1995	9.5	12.9	3.0	6.0
1996	8.0	14.5	3.5	6.5
1997	8.1	12.5	3.3	5.2
1998	8.5	12.5	3.0	5.3
1999	7.9	12.9	2.6	4.3
2000	9.5	11.7	3.1	4.9
2001	8.5	11.8	3.5	4.2
2002	9.9	12.2	3.6	4.1
2003	8.5	9.3	2.5	4.2
2004	8.8	11.1	3.6	4.8
2005	9.7	12.7	3.5	4.9
Slope(b)	**-0.054**	**-0.117**	**-0.034**	**-0.125**
p-value	0.089	**0.002**	0.178	**0.001**

Fig. 4.9(b): STOMACH (ICD-10 : C16) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

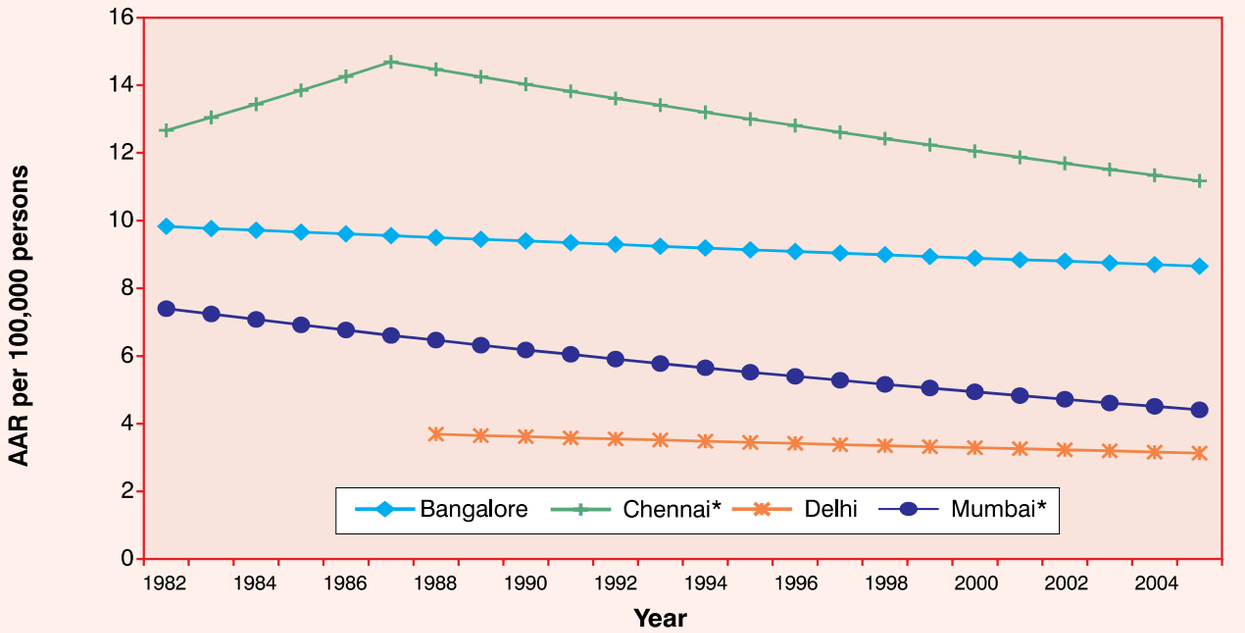


Table 4.9(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	**JP1***	**JP0***	**JP0***
1982	9.8	12.7		7.4
1983	9.8	13.1		7.2
1984	9.7	13.4		7.1
1985	9.7	13.9		6.9
1986	9.6	14.3		6.8
1987	9.6	**14.7**		6.6
1988	9.5	14.5	3.7	6.5
1989	9.5	14.3	3.7	6.3
1990	9.4	14.0	3.6	6.2
1991	9.4	13.8	3.6	6.1
1992	9.3	13.6	3.6	5.9
1993	9.2	13.4	3.5	5.8
1994	9.2	13.2	3.5	5.7
1995	9.1	13.0	3.5	5.5
1996	9.1	12.8	3.4	5.4
1997	9.0	12.6	3.4	5.3
1998	9.0	12.4	3.4	5.2
1999	8.9	12.2	3.3	5.1
2000	8.9	12.1	3.3	4.9
2001	8.8	11.9	3.3	4.8
2002	8.8	11.7	3.2	4.7
2003	8.8	11.5	3.2	4.6
2004	8.7	11.3	3.2	4.5
2005	8.7	11.2	3.1	4.4
APC0	-0.55	**-0.93***	-0.95	**-2.23***
APC1	–	3.00	–	–
APC2	–	**-1.51***	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.10(a): COLON (ICD-10 : C18) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

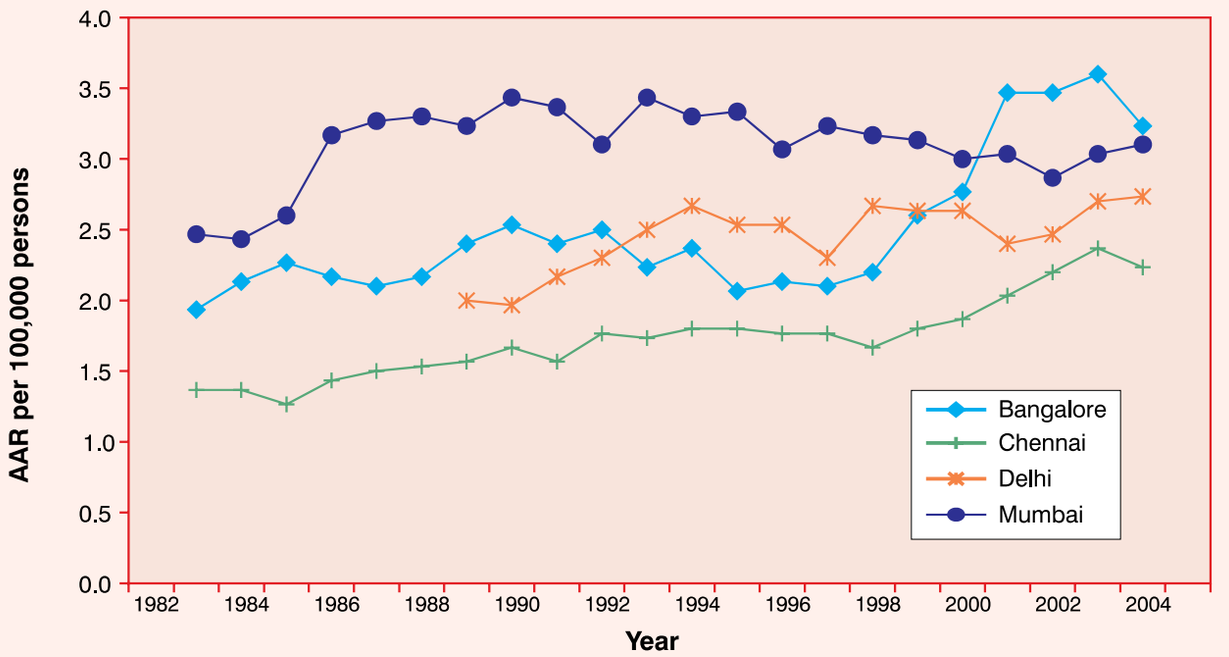


Table 4.10(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	1.8	1.4		2.4
1983	1.8	2.0		2.7
1984	2.2	0.7		2.3
1985	2.4	1.4		2.3
1986	2.2	1.7		3.2
1987	1.9	1.2		4.0
1988	2.2	1.6	2.0	2.6
1989	2.4	1.8	1.9	3.3
1990	2.6	1.3	2.1	3.8
1991	2.6	1.9	1.9	3.2
1992	2.0	1.5	2.5	3.1
1993	2.9	1.9	2.5	3.0
1994	1.8	1.8	2.5	4.2
1995	2.4	1.7	3.0	2.7
1996	2.0	1.9	2.1	3.1
1997	2.0	1.7	2.5	3.4
1998	2.3	1.7	2.3	3.2
1999	2.3	1.6	3.2	2.9
2000	3.2	2.1	2.4	3.3
2001	2.8	1.9	2.3	2.8
2002	4.4	2.1	2.5	3.0
2003	3.2	2.6	2.6	2.8
2004	3.2	2.4	3.0	3.3
2005	3.3	1.7	2.6	3.2
Slope(b)	**0.060**	**0.035**	**0.040**	**0.016**
p-value	**0.001**	**0.001**	**0.013**	0.274

Fig. 4.10(b): COLON (ICD-10 : C18) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

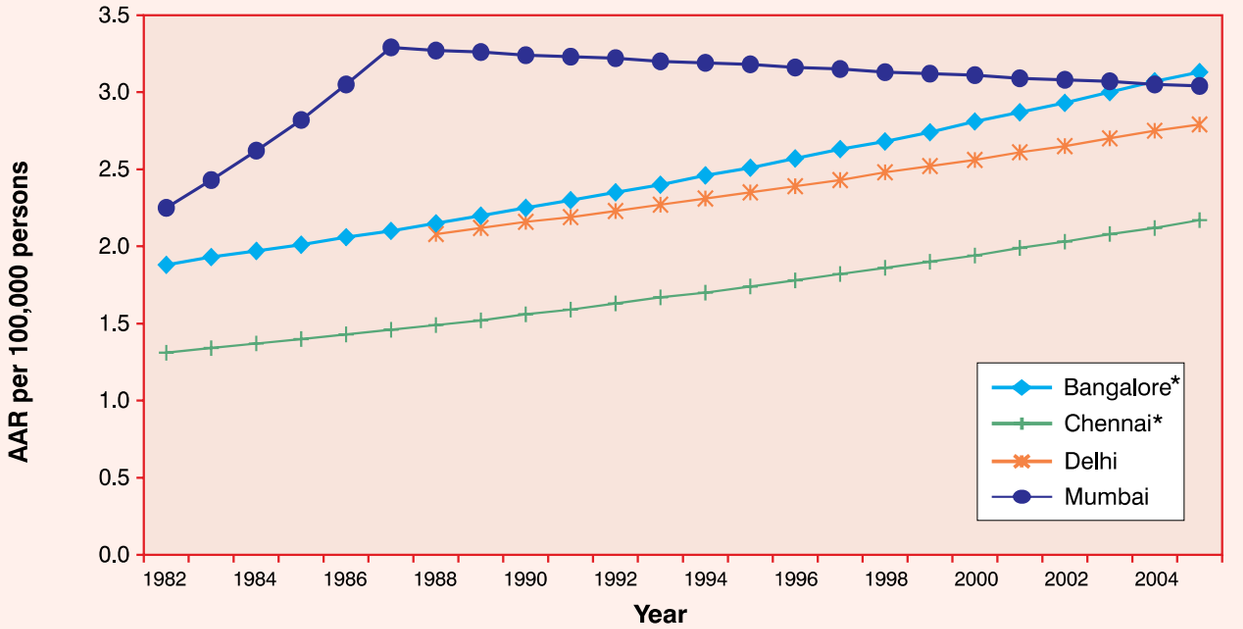


Table 4.10(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	**JP0***	**JP0***	**JP1***
1982	1.9	1.3		2.3
1983	1.9	1.3		2.4
1984	2.0	1.4		2.6
1985	2.0	1.4		2.8
1986	2.1	1.4		3.1
1987	2.1	1.5		**3.3**
1988	2.2	1.5	2.1	3.3
1989	2.2	1.5	2.1	3.3
1990	2.3	1.6	2.2	3.2
1991	2.3	1.6	2.2	3.2
1992	2.4	1.6	2.2	3.2
1993	2.4	1.7	2.3	3.2
1994	2.5	1.7	2.3	3.2
1995	2.5	1.7	2.4	3.2
1996	2.6	1.8	2.4	3.2
1997	2.6	1.8	2.4	3.2
1998	2.7	1.9	2.5	3.1
1999	2.7	1.9	2.5	3.1
2000	2.8	1.9	2.6	3.1
2001	2.9	2.0	2.6	3.1
2002	2.9	2.0	2.7	3.1
2003	3.0	2.1	2.7	3.1
2004	3.1	2.1	2.8	3.1
2005	3.1	2.2	2.8	3.0
APC0	**2.24***	**2.23***	**1.74***	0.63
APC1	–	–	–	7.88
APC2	–	–	–	-0.43

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.11(a): RECTUM (ICD-10 : C19-C20) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

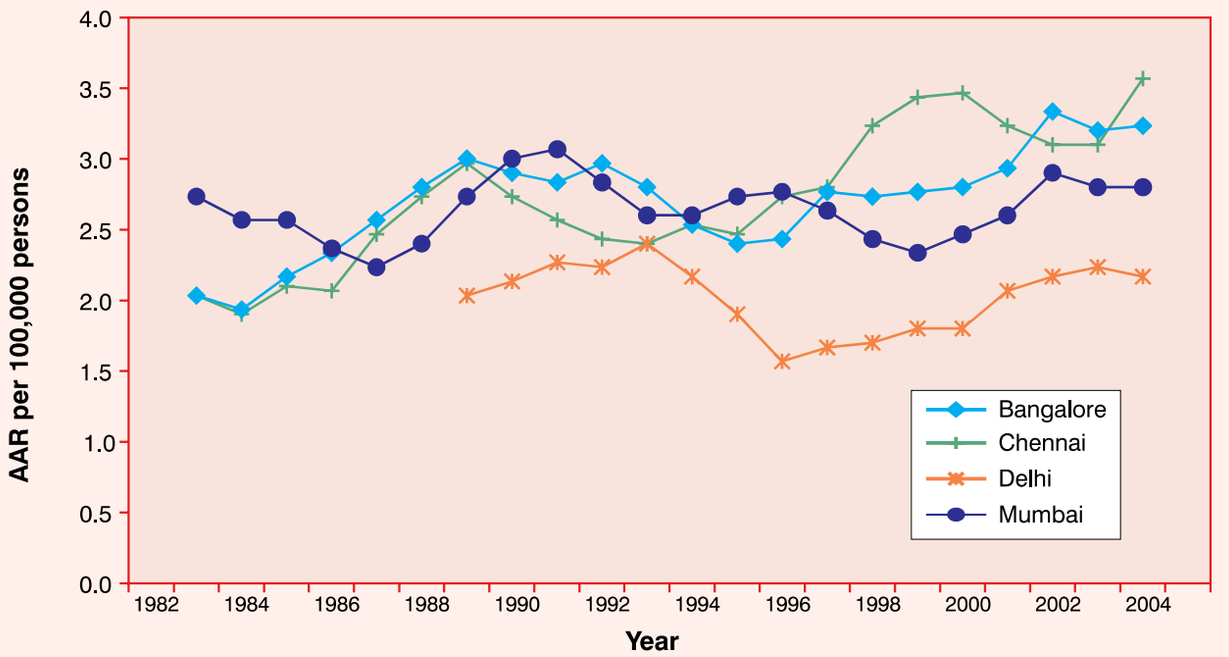


Table 4.11(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	2.5	2.2		3.1
1983	1.8	1.8		2.2
1984	1.8	2.1		2.9
1985	2.2	1.8		2.6
1986	2.5	2.4		2.2
1987	2.3	2.0		2.3
1988	2.9	3.0	1.8	2.2
1989	3.2	3.2	1.9	2.7
1990	2.9	2.7	2.4	3.3
1991	2.6	2.3	2.1	3.0
1992	3.0	2.7	2.3	2.9
1993	3.3	2.3	2.3	2.6
1994	2.1	2.2	2.6	2.3
1995	2.2	3.1	1.6	2.9
1996	2.9	2.1	1.5	3.0
1997	2.2	3.0	1.6	2.4
1998	3.2	3.3	1.9	2.5
1999	2.8	3.4	1.6	2.4
2000	2.3	3.6	1.9	2.1
2001	3.3	3.4	1.9	2.9
2002	3.2	2.7	2.4	2.8
2003	3.5	3.2	2.2	3.0
2004	2.9	3.4	2.1	2.6
2005	3.3	4.1	2.2	2.8
Slope(b)	**0.040**	**0.069**	**-0.001**	**0.004**
p-value	**0.004**	**0.001**	0.973	0.718

Fig. 4.11(b): RECTUM (ICD-10 : C19-C20) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

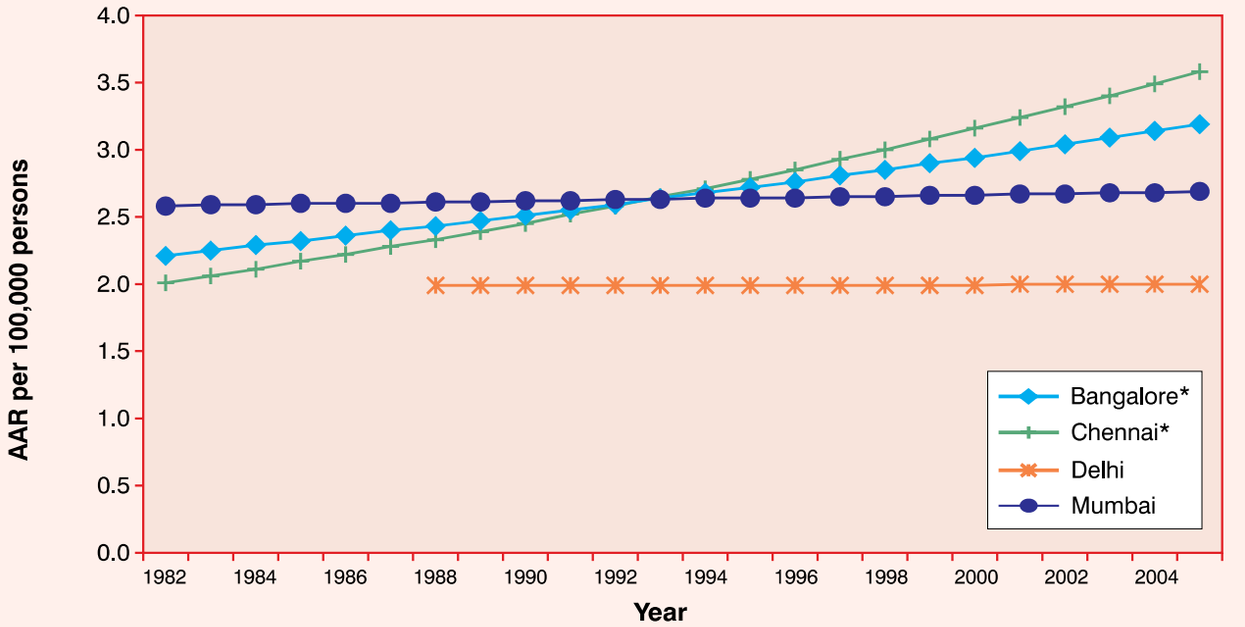


Table 4.11(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*
1982	2.2	2.0		2.6
1983	2.3	2.1		2.6
1984	2.3	2.1		2.6
1985	2.3	2.2		2.6
1986	2.4	2.2		2.6
1987	2.4	2.3		2.6
1988	2.4	2.3	2.0	2.6
1989	2.5	2.4	2.0	2.6
1990	2.5	2.5	2.0	2.6
1991	2.6	2.5	2.0	2.6
1992	2.6	2.6	2.0	2.6
1993	2.6	2.7	2.0	2.6
1994	2.7	2.7	2.0	2.6
1995	2.7	2.8	2.0	2.6
1996	2.8	2.9	2.0	2.6
1997	2.8	2.9	2.0	2.7
1998	2.9	3.0	2.0	2.7
1999	2.9	3.1	2.0	2.7
2000	2.9	3.2	2.0	2.7
2001	3.0	3.2	2.0	2.7
2002	3.0	3.3	2.0	2.7
2003	3.1	3.4	2.0	2.7
2004	3.1	3.5	2.0	2.7
2005	3.2	3.6	2.0	2.7
APC0	1.60*	2.54*	0.04	0.00
APC1	–	–	–	0.17
APC2	–	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.12(a): LIVER (ICD-10 : C22) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

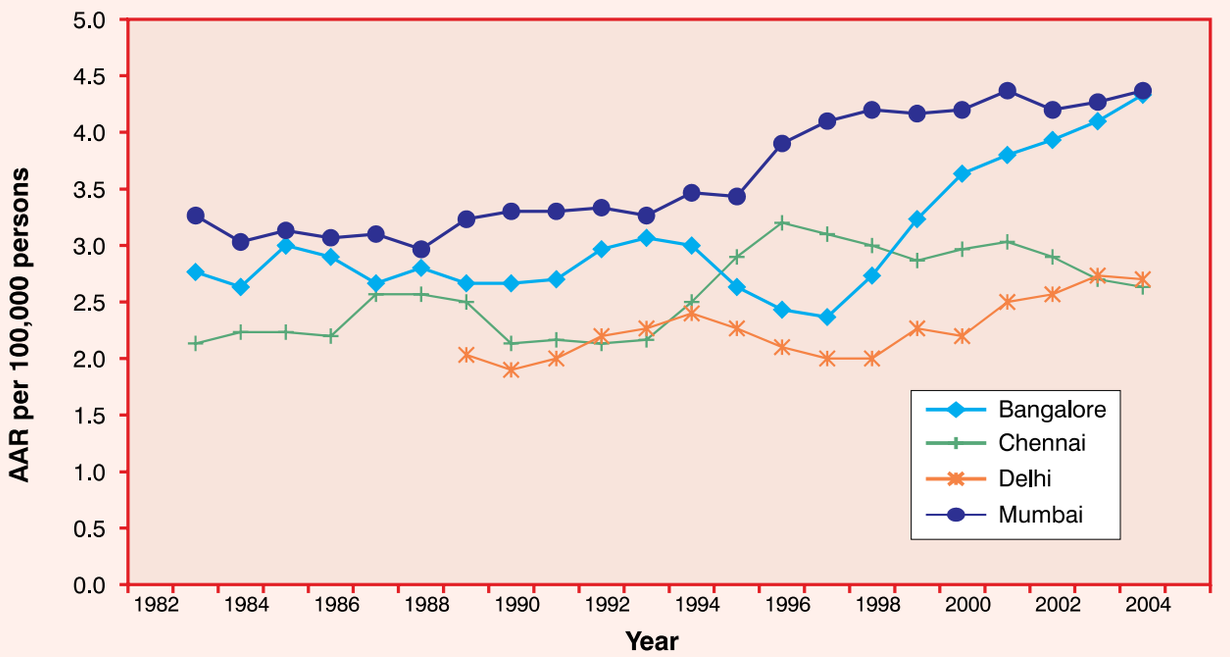


Table 4.12(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	3.6	1.8		3.7
1983	1.4	1.4		3.1
1984	3.3	2.4		3.0
1985	3.2	2.3		3.0
1986	2.5	1.9		3.4
1987	3.0	2.3		2.8
1988	2.5	3.4	2.3	3.1
1989	2.9	1.6	2.0	3.0
1990	2.6	2.1	1.8	3.6
1991	2.5	2.3	1.9	3.3
1992	3.0	2.0	2.3	3.0
1993	3.4	1.6	2.4	3.7
1994	2.8	2.4	2.1	3.1
1995	2.8	3.0	2.7	3.6
1996	2.3	3.2	2.0	3.6
1997	2.2	3.3	1.6	4.5
1998	2.6	2.8	2.4	4.2
1999	3.4	2.9	2.0	3.9
2000	3.7	2.9	2.4	4.4
2001	3.8	3.1	2.2	4.3
2002	3.9	3.0	2.9	4.4
2003	4.1	2.5	2.6	3.9
2004	4.3	2.5	2.7	4.5
2005	4.6	2.9	2.8	4.7
Slope(b)	**0.061**	**0.048**	**0.039**	**0.068**
p-value	**0.003**	**0.002**	**0.011**	**0.001**

Fig. 4.12(b): LIVER (ICD-10 : C22) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

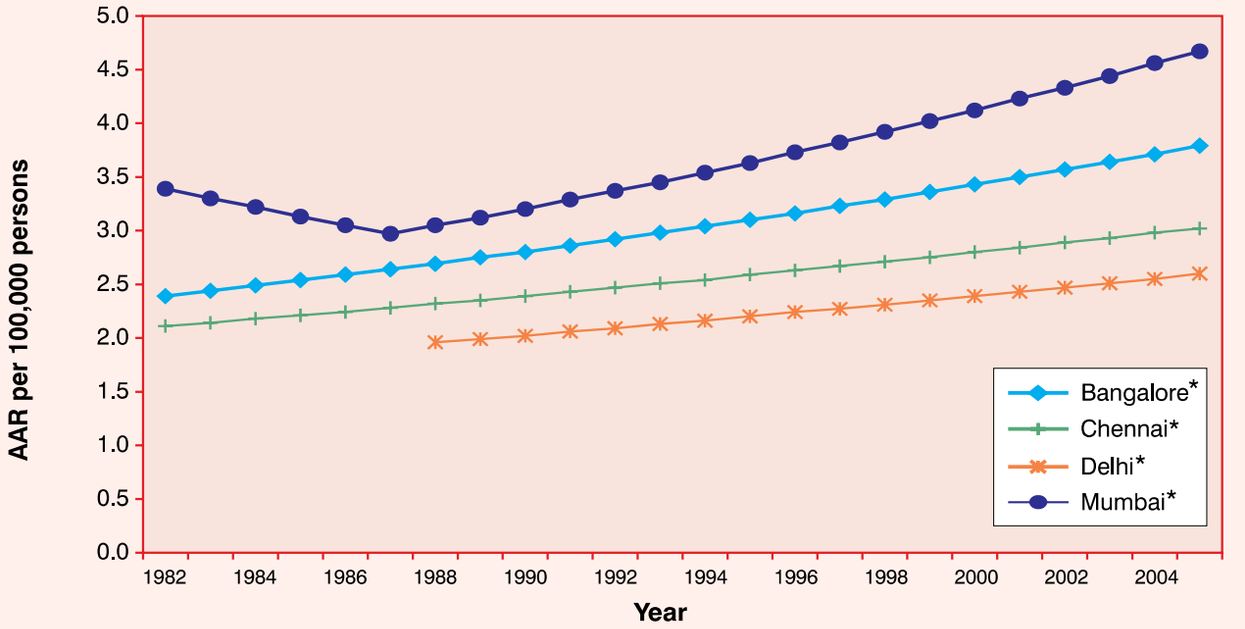


Table 4.12(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	**JP0***	**JP0***	**JP1***
1982	2.4	2.1		3.4
1983	2.4	2.1		3.3
1984	2.5	2.2		3.2
1985	2.5	2.2		3.1
1986	2.6	2.2		3.1
1987	2.6	2.3		**3.0**
1988	2.7	2.3	2.0	3.1
1989	2.8	2.4	2.0	3.1
1990	2.8	2.4	2.0	3.2
1991	2.9	2.4	2.1	3.3
1992	2.9	2.5	2.1	3.4
1993	3.0	2.5	2.1	3.5
1994	3.0	2.5	2.2	3.5
1995	3.1	2.6	2.2	3.6
1996	3.2	2.6	2.2	3.7
1997	3.2	2.7	2.3	3.8
1998	3.3	2.7	2.3	3.9
1999	3.4	2.8	2.4	4.0
2000	3.4	2.8	2.4	4.1
2001	3.5	2.8	2.4	4.2
2002	3.6	2.9	2.5	4.3
2003	3.6	2.9	2.5	4.4
2004	3.7	3.0	2.6	4.6
2005	3.8	3.0	2.6	4.7
APC0	**2.02***	**1.58***	**1.67***	**1.85***
APC1	–	–	–	-2.61
APC2	–	–	–	**2.55***

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.13(a): GALLBLADDER (ICD-10 : C23-C24) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

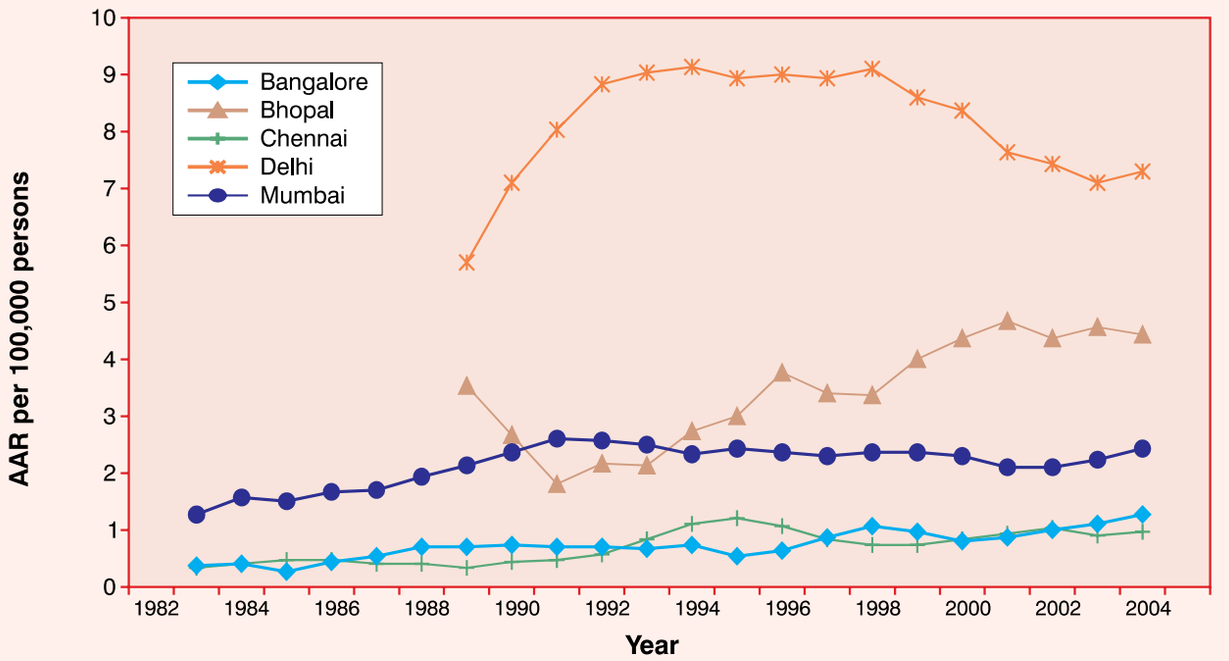


Table 4.13(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	0.0		0.2		0.9
1983	0.6		0.3		1.6
1984	0.3		0.5		1.3
1985	0.3		0.4		1.8
1986	0.2		0.5		1.4
1987	0.8		0.5		1.8
1988	0.6	4.1	0.2	4.2	1.9
1989	0.7	4.8	0.5	6.2	2.1
1990	0.8	1.7	0.3	6.7	2.4
1991	0.7	1.5	0.5	8.4	2.6
1992	0.6	2.2	0.6	9.0	2.8
1993	0.8	2.8	0.6	9.1	2.3
1994	0.6	1.4	1.3	9.0	2.4
1995	0.8	4.0	1.4	9.3	2.3
1996	0.2	3.6	0.9	8.5	2.6
1997	0.9	3.7	0.9	9.2	2.2
1998	1.5	2.9	0.7	9.1	2.1
1999	0.8	3.5	0.6	9.0	2.8
2000	0.6	5.6	0.9	7.7	2.2
2001	1.0	4.0	1.0	8.4	1.9
2002	1.0	4.4	0.9	6.8	2.2
2003	1.0	4.7	1.2	7.1	2.2
2004	1.3	4.6	0.6	7.4	2.3
2005	1.5	4.0	1.1	7.4	2.8
Slope(b)	**0.040**	**0.114**	**0.034**	**0.045**	**0.044**
p-value	**0.001**	**0.033**	**0.001**	0.477	**0.001**

Fig. 4.13(b): GALLBLADDER (ICD-10 : C23-C24) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

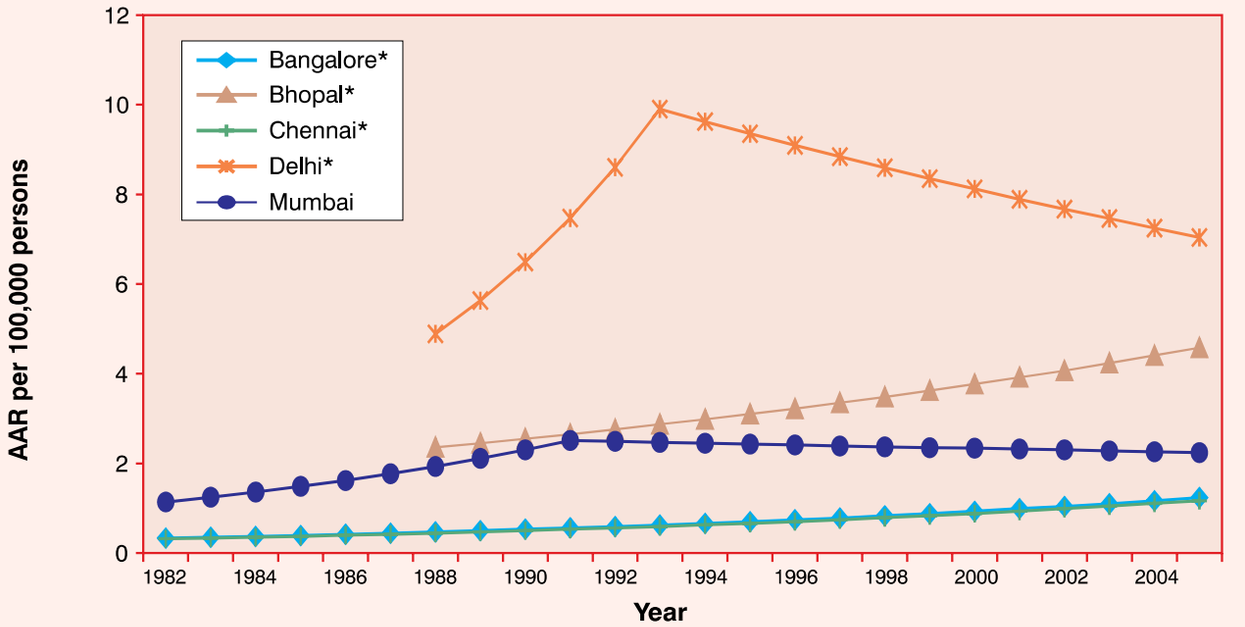


Table 4.13(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore[$]	Bhopal	Chennai[$]	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP1*	JP1*
1982	0.3		0.3		1.1
1983	0.4		0.3		1.3
1984	0.4		0.4		1.4
1985	0.4		0.4		1.5
1986	0.4		0.4		1.6
1987	0.4		0.4		1.8
1988	0.5	2.4	0.4	4.9	1.9
1989	0.5	2.5	0.5	5.6	2.1
1990	0.5	2.6	0.5	6.5	2.3
1991	0.6	2.7	0.5	7.5	**2.5**
1992	0.6	2.8	0.6	8.6	2.5
1993	0.6	2.9	0.6	**9.9**	2.5
1994	0.7	3.0	0.6	9.6	2.5
1995	0.7	3.1	0.7	9.4	2.4
1996	0.7	3.2	0.7	9.1	2.4
1997	0.8	3.4	0.7	8.8	2.4
1998	0.8	3.5	0.8	8.6	2.4
1999	0.9	3.6	0.8	8.4	2.4
2000	0.9	3.8	0.9	8.1	2.3
2001	1.0	3.9	0.9	7.9	2.3
2002	1.0	4.1	1.0	7.7	2.3
2003	1.1	4.2	1.1	7.5	2.3
2004	1.2	4.4	1.1	7.3	2.3
2005	1.2	4.6	1.2	7.0	2.2
APC0	**5.88***	**3.99***	**5.87***	0.93	**2.53***
APC1	–	–	–	**15.13***	**9.14***
APC2	–	–	–	**-2.79***	-0.8

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*
[$] Kindly note the trend values in the 2 PBCRs are identical and therefore only one line is visible in the graph.

Fig. 4.14(a): LARYNX (ICD-10 : C32) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

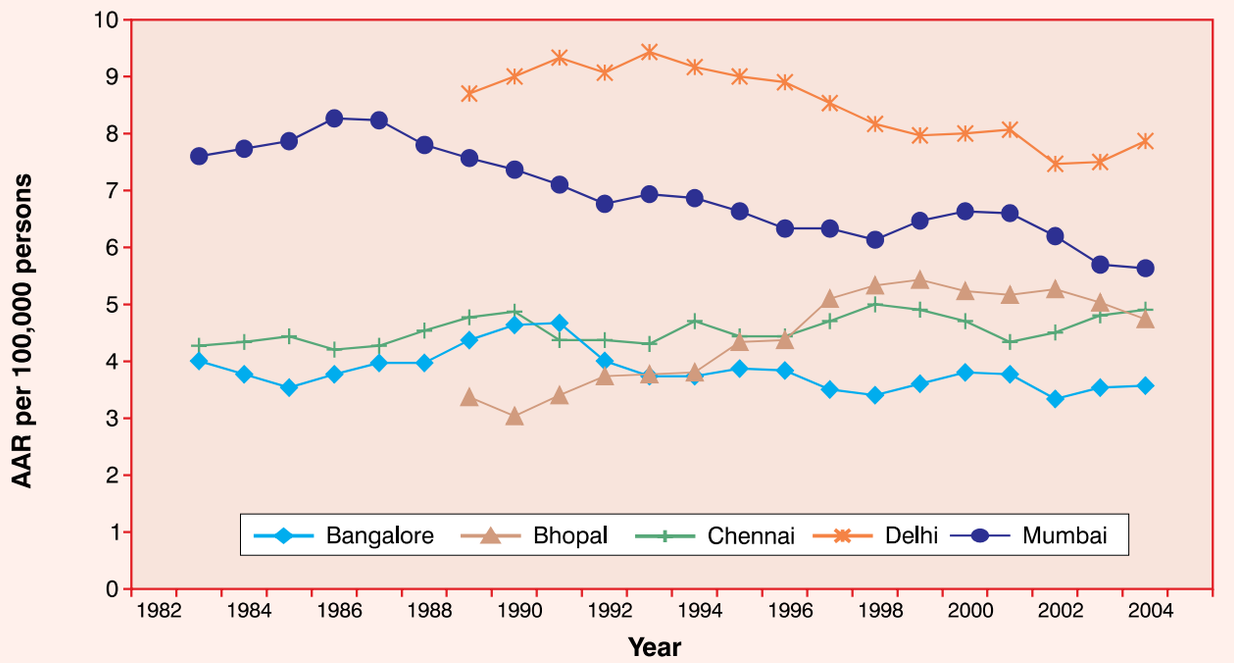


Table 4.14(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	4.0		4.2		6.7
1983	4.4		3.7		8.5
1984	3.6		4.9		7.6
1985	3.3		4.4		7.1
1986	3.7		4.0		8.9
1987	4.3		4.2		8.8
1988	3.9	5.1	4.6	7.4	7.0
1989	3.7	2.6	4.8	8.3	7.6
1990	5.5	2.4	4.9	10.4	8.1
1991	4.7	4.1	4.9	8.3	6.4
1992	3.8	3.7	3.3	9.3	6.8
1993	3.5	3.4	4.9	9.6	7.1
1994	3.9	4.2	4.7	9.4	6.9
1995	3.8	3.8	4.5	8.5	6.6
1996	3.9	5.0	4.1	9.1	6.4
1997	3.8	4.3	4.7	9.1	6.0
1998	2.8	6.0	5.3	7.4	6.6
1999	3.6	5.7	5.0	8.0	5.8
2000	4.4	4.6	4.4	8.5	7.0
2001	3.4	5.4	4.7	7.5	7.1
2002	3.5	5.5	3.9	8.2	5.7
2003	3.1	4.9	4.9	6.7	5.8
2004	4.0	4.7	5.6	7.6	5.6
2005	3.6	4.6	4.2	9.3	5.5
Slope(b)	**-0.024**	**0.111**	**0.024**	**-0.062**	**-0.102**
p-value	0.140	**0.010**	0.118	0.160	**0.001**

Fig. 4.14(b): LARYNX (ICD-10 : C32) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

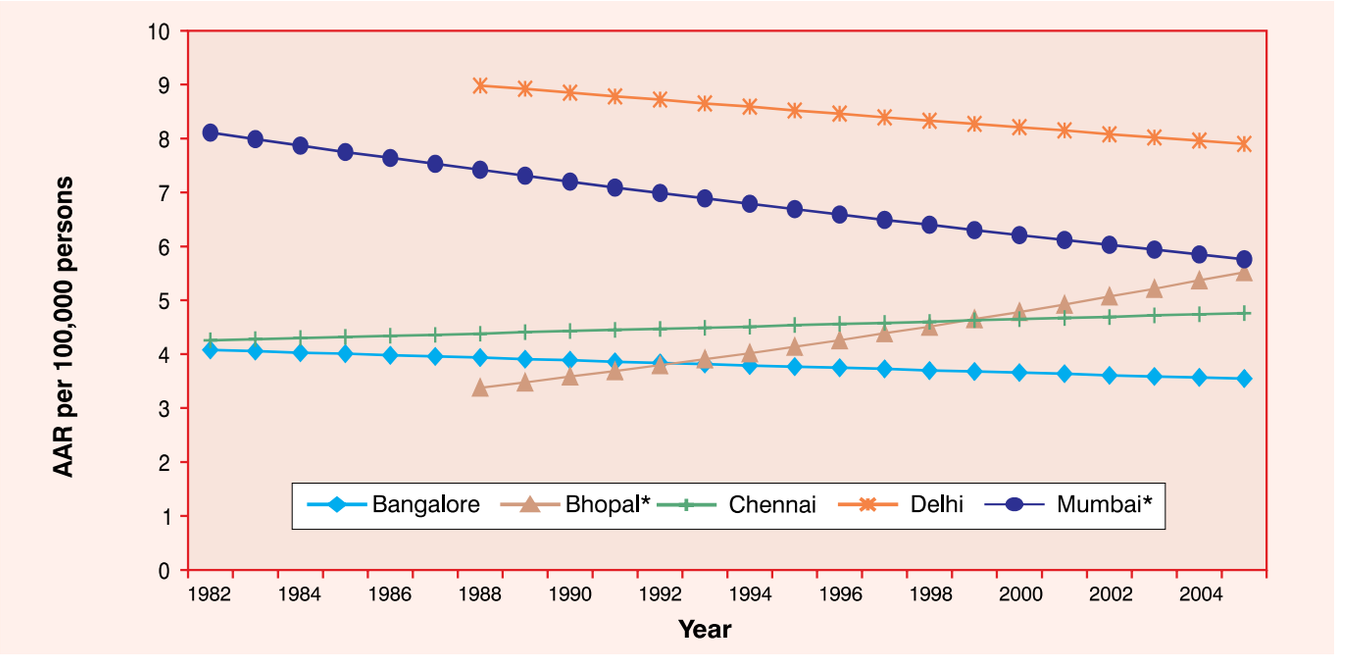


Table 4.14(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*	JP0*
1982	4.1		4.3		8.1
1983	4.1		4.3		8.0
1984	4.0		4.3		7.9
1985	4.0		4.3		7.8
1986	4.0		4.3		7.6
1987	4.0		4.4		7.5
1988	3.9	3.4	4.4	9.0	7.4
1989	3.9	3.5	4.4	8.9	7.3
1990	3.9	3.6	4.4	8.9	7.2
1991	3.9	3.7	4.5	8.8	7.1
1992	3.8	3.8	4.5	8.7	7.0
1993	3.8	3.9	4.5	8.7	6.9
1994	3.8	4.0	4.5	8.6	6.8
1995	3.8	4.1	4.5	8.5	6.7
1996	3.8	4.3	4.6	8.5	6.6
1997	3.7	4.4	4.6	8.4	6.5
1998	3.7	4.5	4.6	8.3	6.4
1999	3.7	4.7	4.6	8.3	6.3
2000	3.7	4.8	4.7	8.2	6.2
2001	3.6	4.9	4.7	8.2	6.1
2002	3.6	5.1	4.7	8.1	6.0
2003	3.6	5.2	4.7	8.0	5.9
2004	3.6	5.4	4.7	8.0	5.9
2005	3.6	5.5	4.8	7.9	5.8
APC0	-0.61	**2.92***	0.49	-0.75	**-1.47***
APC1	–	–	–	–	–
APC2	–	–	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.15(a): LUNG (ICD-10 : C33-C34) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

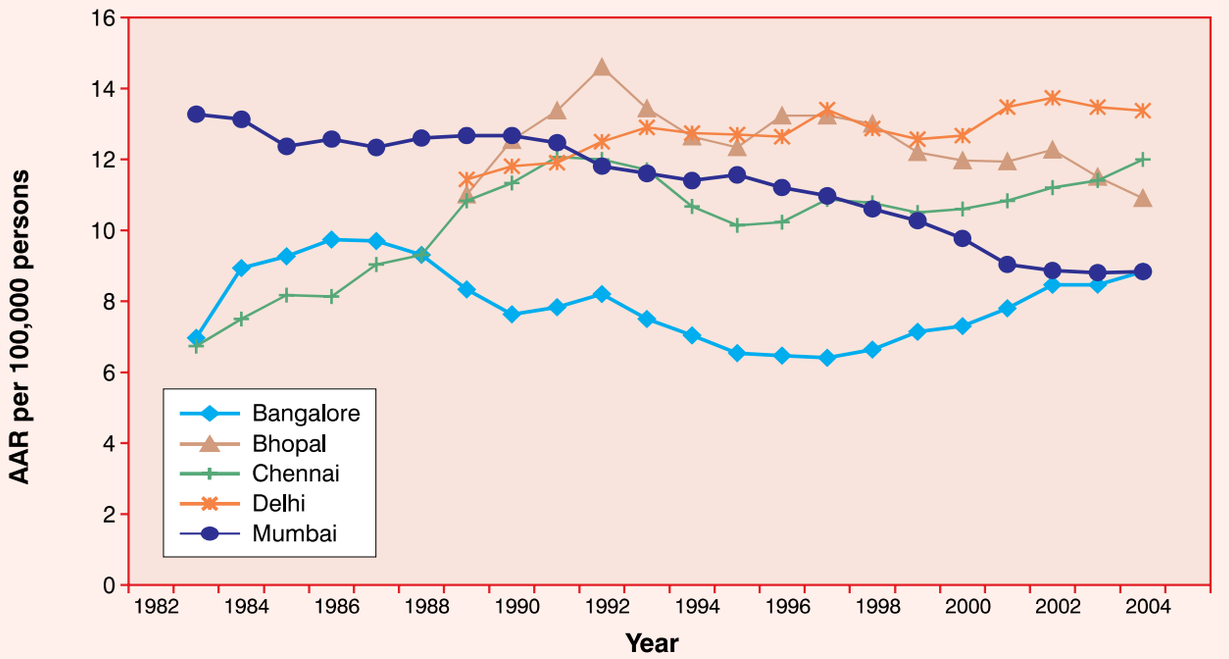


Table 4.15(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	4.7		5.0		13.3
1983	7.9		7.1		14.0
1984	8.3		8.1		12.5
1985	10.6		7.3		12.9
1986	8.9		9.1		11.7
1987	9.7		8.0		13.1
1988	10.5	10.1	10.0	10.5	12.2
1989	7.7	12.5	9.9	11.3	12.5
1990	6.8	10.4	12.6	12.0	13.3
1991	8.4	14.7	11.5	12.1	12.2
1992	8.3	15.0	12.1	11.6	11.9
1993	7.9	14.1	12.4	13.8	11.3
1994	6.3	11.2	10.6	13.3	11.6
1995	6.9	12.6	9.0	11.1	11.3
1996	6.4	13.2	10.8	13.7	11.8
1997	6.1	13.9	10.9	13.1	10.5
1998	6.7	12.6	10.9	13.4	10.6
1999	7.1	12.5	10.5	12.1	10.7
2000	7.6	11.5	10.1	12.2	9.5
2001	7.2	11.9	11.2	13.7	9.1
2002	8.6	12.4	11.2	14.5	8.5
2003	9.6	12.5	11.2	13.0	9.0
2004	7.2	9.6	11.8	12.9	8.9
2005	9.7	10.6	13.0	14.2	8.6
Slope(b)	**-0.013**	**-0.075**	**0.198**	**0.139**	**-0.217**
p-value	0.776	0.306	**0.001**	**0.004**	**0.001**

Fig. 4.15(b): LUNG (ICD-10 : C33-C34) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

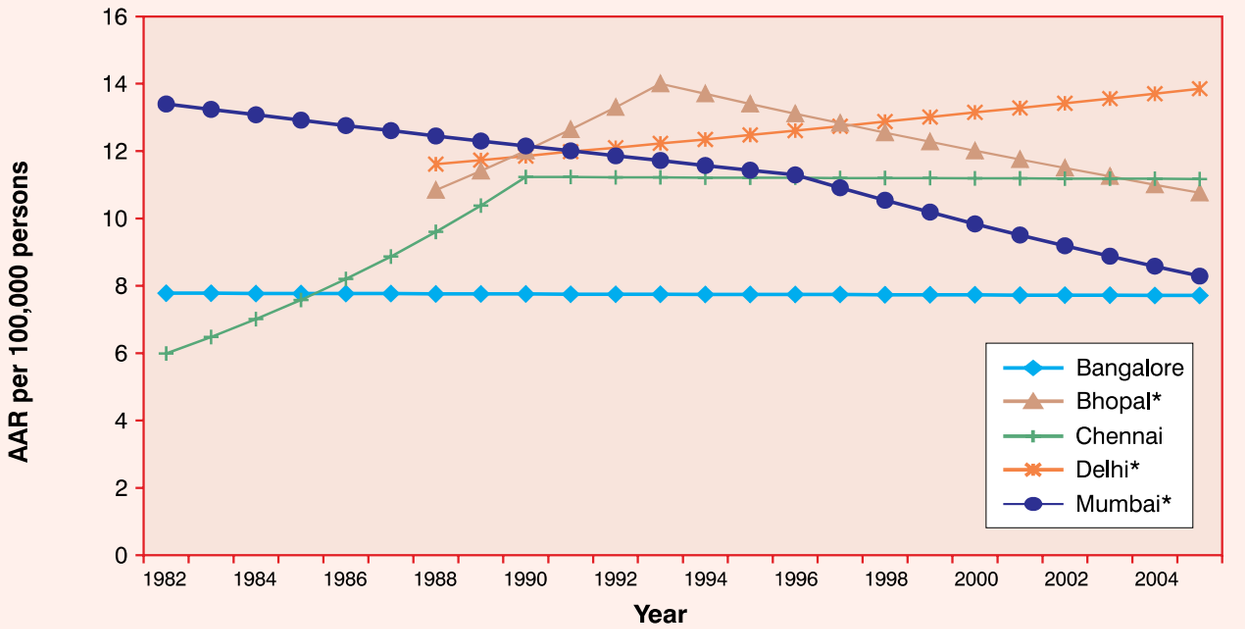


Table 4.15(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	**JP1***	**JP1***	**JP0***	**JP1***
1982	7.8		6.0		13.4
1983	7.8		6.5		13.2
1984	7.8		7.0		13.1
1985	7.8		7.6		12.9
1986	7.8		8.2		12.8
1987	7.8		8.9		12.6
1988	7.8	10.8	9.6	11.6	12.5
1989	7.8	11.4	10.4	11.7	12.3
1990	7.8	12.0	**11.2**	11.9	12.2
1991	7.8	12.6	11.2	12.0	12.0
1992	7.8	13.3	11.2	12.1	11.9
1993	7.8	**14.0**	11.2	12.2	11.7
1994	7.7	13.7	11.2	12.4	11.6
1995	7.7	13.4	11.2	12.5	11.4
1996	7.7	13.1	11.2	12.6	**11.3**
1997	7.7	12.8	11.2	12.7	10.9
1998	7.7	12.6	11.2	12.9	10.5
1999	7.7	12.3	11.2	13.0	10.2
2000	7.7	12.0	11.2	13.2	9.8
2001	7.7	11.8	11.2	13.3	9.5
2002	7.7	11.5	11.2	13.4	9.2
2003	7.7	11.3	11.2	13.6	8.9
2004	7.7	11.0	11.2	13.7	8.6
2005	7.7	10.8	11.2	13.9	8.3
APC0	-0.04	-0.57	**2.25***	**1.04***	**-1.97***
APC1	–	5.25	**8.16***	–	**-1.22***
APC2	–	**-2.17***	-0.03	–	**-3.38***

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.16(a): LUNG (ICD-10 : C33-C34) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

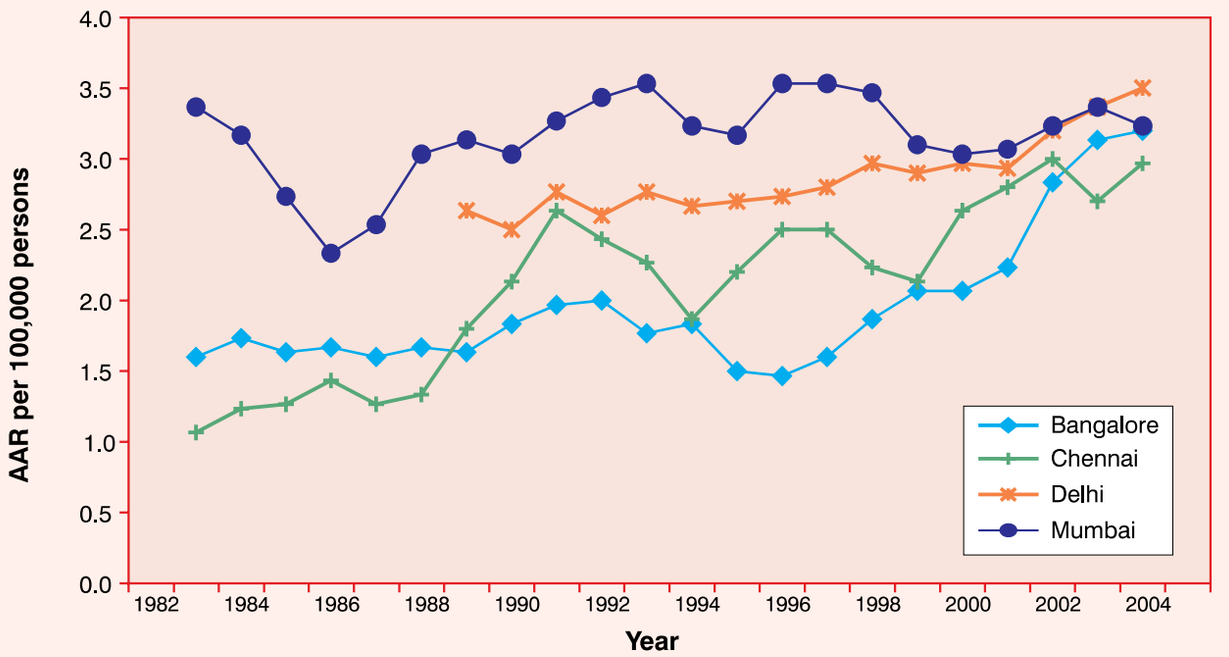


Table 4.16(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	1.2	1.1		3.2
1983	1.6	1.3		3.1
1984	2.0	0.8		3.8
1985	1.6	1.6		2.6
1986	1.3	1.4		1.8
1987	2.1	1.3		2.6
1988	1.4	1.1	2.6	3.2
1989	1.5	1.6	2.1	3.3
1990	2.0	2.7	3.2	2.9
1991	2.0	2.1	2.2	2.9
1992	1.9	3.1	2.9	4.0
1993	2.1	2.1	2.7	3.4
1994	1.3	1.6	2.7	3.2
1995	2.1	1.9	2.6	3.1
1996	1.1	3.1	2.8	3.2
1997	1.2	2.5	2.8	4.3
1998	2.5	1.9	2.8	3.1
1999	1.9	2.3	3.3	3.0
2000	1.8	2.2	2.6	3.2
2001	2.5	3.4	3.0	2.9
2002	2.4	2.8	3.2	3.1
2003	3.6	2.8	3.4	3.7
2004	3.4	2.5	3.5	3.3
2005	2.6	3.6	3.6	2.7
Slope(b)	**0.057**	**0.087**	**0.056**	**0.012**
p-value	**0.023**	**0.001**	**0.001**	0.421

Fig. 4.16(b): LUNG (ICD-10 : C33-C34) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

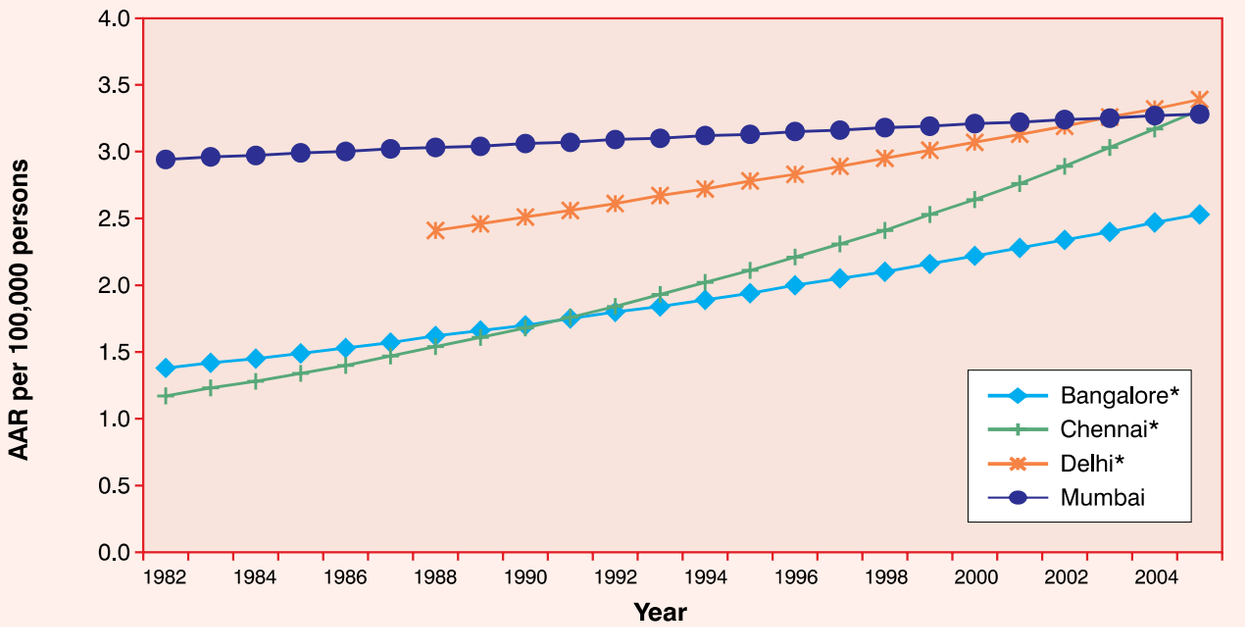


Table 4.16(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*
1982	1.4	1.2		2.9
1983	1.4	1.2		3.0
1984	1.5	1.3		3.0
1985	1.5	1.3		3.0
1986	1.5	1.4		3.1
1987	1.6	1.5		3.0
1988	1.6	1.5	2.4	3.0
1989	1.7	1.6	2.5	3.0
1990	1.7	1.7	2.5	3.1
1991	1.8	1.8	2.6	3.1
1992	1.8	1.8	2.6	3.1
1993	1.8	1.9	2.7	3.1
1994	1.9	2.0	2.7	3.1
1995	1.9	2.1	2.8	3.1
1996	2.0	2.2	2.8	3.2
1997	2.1	2.3	2.9	3.2
1998	2.1	2.4	3.0	3.2
1999	2.2	2.5	3.0	3.2
2000	2.2	2.6	3.1	3.2
2001	2.3	2.8	3.1	3.2
2002	2.3	2.9	3.2	3.2
2003	2.4	3.0	3.3	3.3
2004	2.5	3.2	3.3	3.3
2005	2.5	3.3	3.4	3.3
APC0	2.67*	4.62*	2.02*	0.47
APC1	–	–	–	–
APC2	–	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.17(a): BREAST (ICD-10 : C50) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

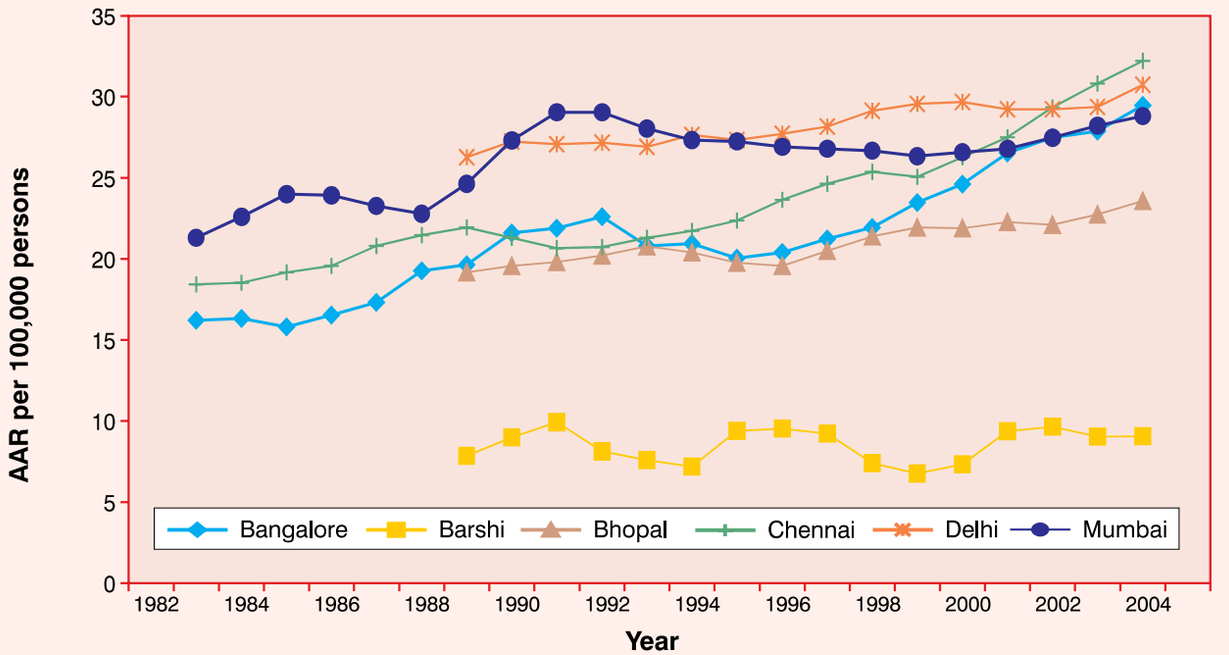


Table 4.17(a): Year wise AARs

Year	Bangalore	Barshi	Bhopal	Chennai	Delhi	Mumbai
1982	15.8			18.4		20.8
1983	16.0			18.2		20.7
1984	16.8			18.7		22.4
1985	16.2			18.7		24.7
1986	14.4			20.1		24.9
1987	19.0			19.9		22.2
1988	18.6	7.2	18.2	22.4	24.8	22.7
1989	20.2	6.6	19.5	22.1	26.9	23.5
1990	20.1	9.8	19.8	21.3	27.1	27.7
1991	24.5	10.6	19.4	20.5	27.7	30.7
1992	21.1	9.4	20.2	20.2	26.4	28.7
1993	22.2	4.4	21.0	21.5	27.4	27.7
1994	19.1	9.0	21.1	22.2	26.9	27.7
1995	21.5	8.2	19.1	21.5	28.6	26.6
1996	19.5	11.0	19.1	23.4	26.5	27.4
1997	20.2	9.4	20.5	26.0	28.0	26.7
1998	24.0	7.3	21.9	24.5	30.0	26.3
1999	21.6	5.5	21.8	25.6	29.4	27.0
2000	24.8	7.5	22.1	25.1	29.3	25.7
2001	27.4	9.0	21.8	28.1	30.3	27.0
2002	27.4	11.6	22.9	29.3	28.1	27.7
2003	27.6	8.4	21.6	30.6	29.3	27.7
2004	28.6	7.1	23.7	32.5	30.7	29.2
2005	32.2	11.7	25.4	33.5	32.2	29.5
Slope(b)	**0.587**	**0.074**	**0.293**	**0.587**	**0.292**	**0.283**
p-value	**0.001**	0.438	**0.001**	**0.001**	**0.001**	**0.001**

Fig. 4.17(b): BREAST (ICD-10 : C50) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

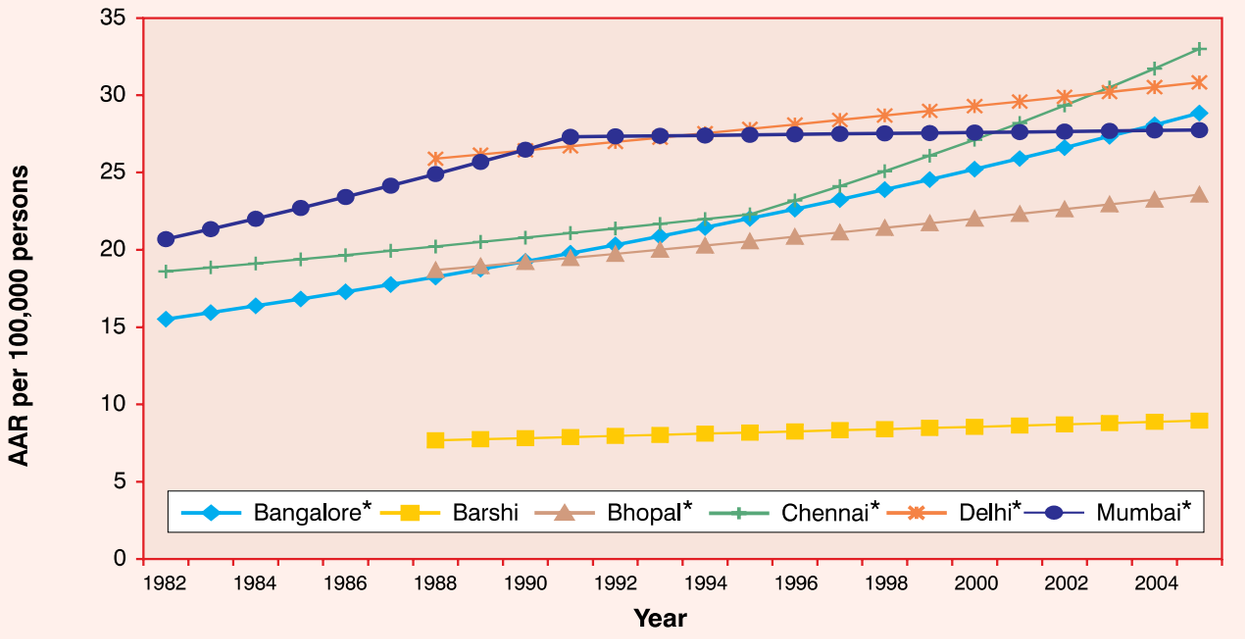


Table 4.17(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Barshi	Bhopal	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP1*	JP0*	JP1*
1982	15.5			18.6		20.7
1983	15.9			18.9		21.3
1984	16.4			19.1		22.0
1985	16.8			19.4		22.7
1986	17.3			19.7		23.4
1987	17.8			19.9		24.1
1988	18.2	7.7	18.7	20.2	26.0	24.9
1989	18.7	7.8	19.0	20.5	26.2	25.7
1990	19.3	7.8	19.2	20.8	26.4	26.5
1991	19.8	7.9	19.5	21.1	26.7	**27.3**
1992	20.3	8.0	19.7	21.4	27.0	27.3
1993	20.9	8.0	20.0	21.7	27.3	27.4
1994	21.4	8.1	20.3	22.0	27.5	27.4
1995	22.0	8.2	20.6	**22.3**	27.8	27.4
1996	22.6	8.3	20.9	23.2	28.1	27.5
1997	23.3	8.3	21.1	24.1	28.4	27.5
1998	23.9	8.4	21.4	25.1	28.7	27.5
1999	24.5	8.5	21.7	26.1	29.0	27.6
2000	25.2	8.6	22.0	27.1	29.3	27.6
2001	25.9	8.6	22.3	28.2	29.6	27.6
2002	26.6	8.7	22.6	29.3	29.9	27.7
2003	27.3	8.8	22.9	30.5	30.2	27.7
2004	28.1	8.9	23.3	31.7	30.5	27.7
2005	28.9	9.0	23.6	33.0	30.8	27.8
APC0	2.73*	0.9	1.38*	2.45*	1.03*	1.15*
APC1	–	–	–	1.40*	–	3.13*
APC2	–	–	–	4.00*	–	0.11

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.18(a): CERVIX (ICD-10 : C53) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

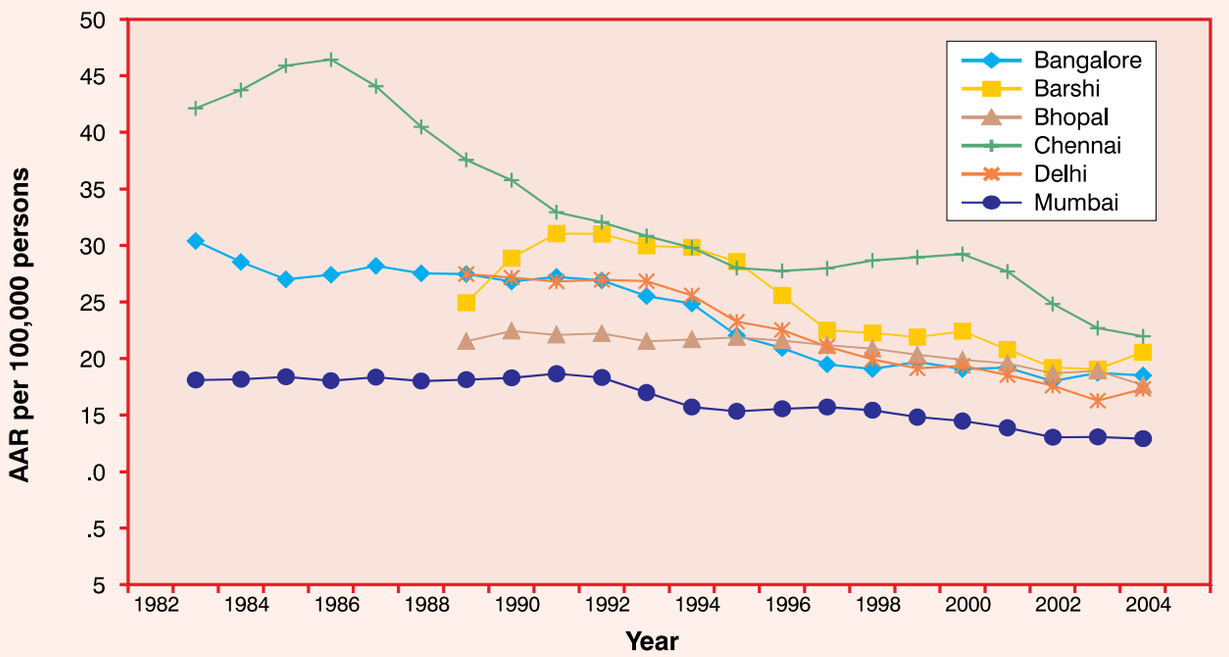


Table 4.18(a): Year wise AARs

Year	Bangalore	Barshi	Bhopal	Chennai	Delhi	Mumbai
1982	32.4			41.0		17.9
1983	30.6			43.5		17.8
1984	28.2			41.9		18.6
1985	26.8			45.8		18.1
1986	26.0			50.0		18.4
1987	29.4			43.5		17.6
1988	29.2	22.1	21.7	38.8	25.9	19.0
1989	24.0	24.9	21.8	39.2	28.4	17.4
1990	29.2	27.8	21.1	34.7	28.1	18.0
1991	27.2	34.0	24.4	33.4	25.0	19.4
1992	25.3	31.4	20.8	30.7	27.3	18.6
1993	28.2	27.7	21.4	32.1	28.6	16.9
1994	23.1	30.8	22.4	29.7	24.6	15.5
1995	23.3	31.0	21.2	27.6	23.5	14.7
1996	19.7	23.9	22.0	26.7	21.7	15.8
1997	19.8	21.8	21.6	29.0	22.4	16.1
1998	18.9	21.8	19.9	28.2	19.1	15.2
1999	18.5	23.1	21.1	28.8	18.3	15.0
2000	21.7	20.8	20.0	29.8	20.0	14.3
2001	17.0	23.3	18.6	29.1	19.8	14.1
2002	18.9	18.3	20.1	24.2	15.8	13.2
2003	18.1	16.0	17.4	21.2	17.2	11.8
2004	19.2	22.9	19.2	22.7	15.8	14.2
2005	18.2	22.7	16.4	22.0	18.9	12.7
Slope	**-0.611**	**-0.554**	**-0.271**	**-1.051**	**-0.747**	**-0.271**
p-value	**0.001**	**0.007**	**0.001**	**0.001**	**0.001**	**0.001**

Fig. 4.18(b): CERVIX (ICD-10 : C53) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

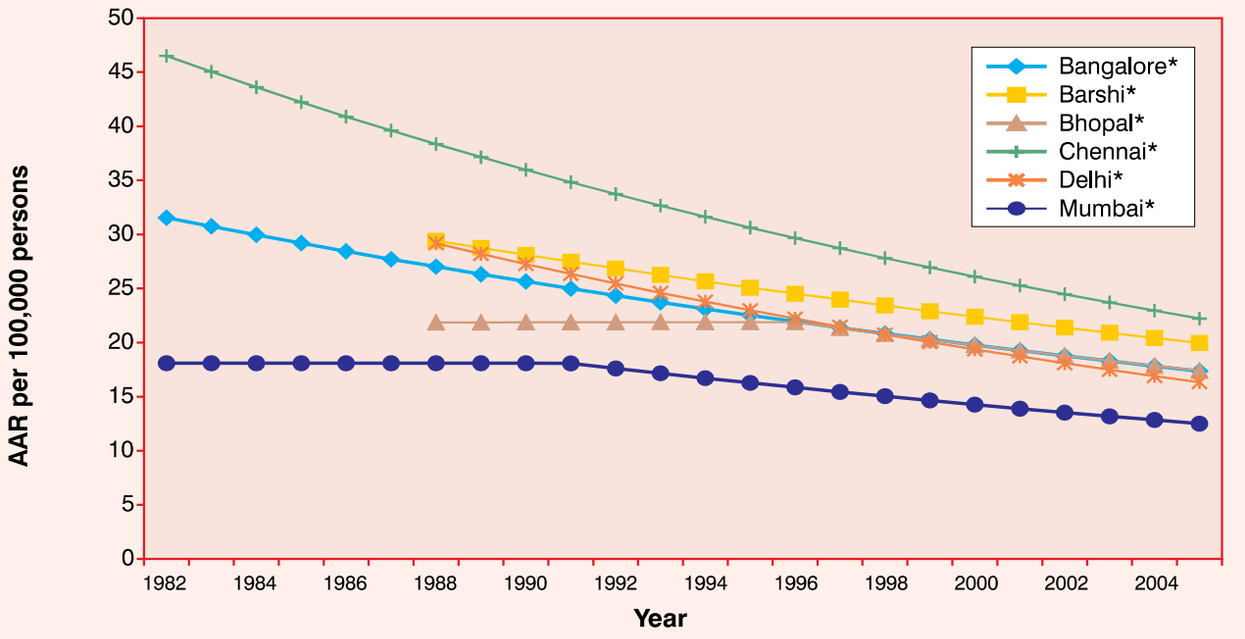


Table 4.18(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Barshi	Bhopal	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP1*	JP0*	JP0*	JP1*
1982	31.6			46.5		18.1
1983	30.8			45.0		18.1
1984	30.0			43.6		18.1
1985	29.2			42.2		18.1
1986	28.4			40.9		18.1
1987	27.7			39.6		18.1
1988	27.0	29.4	21.9	38.4	29.2	18.1
1989	26.3	28.8	21.9	37.1	28.2	18.1
1990	25.6	28.1	21.9	36.0	27.3	18.1
1991	25.0	27.5	21.9	34.8	26.3	**18.1**
1992	24.3	26.9	21.9	33.7	25.5	17.6
1993	23.7	26.3	21.9	32.7	24.6	17.2
1994	23.1	25.7	21.9	31.6	23.8	16.7
1995	22.5	25.1	**21.9**	30.6	23.0	16.3
1996	21.9	24.5	21.9	29.7	22.2	15.9
1997	21.4	24.0	21.3	28.7	21.5	15.4
1998	20.8	23.4	20.8	27.8	20.8	15.0
1999	20.3	22.9	20.3	26.9	20.1	14.7
2000	19.8	22.4	19.8	26.1	19.4	14.3
2001	19.3	21.9	19.3	25.3	18.7	13.9
2002	18.8	21.4	18.8	24.5	18.1	13.5
2003	18.3	20.9	18.3	23.7	17.5	13.2
2004	17.8	20.4	17.9	23.0	16.9	12.8
2005	17.4	20.0	17.4	22.2	16.3	12.5
APC0	-2.56*	-2.25*	-1.36*	-3.16*	-3.35*	-1.71*
APC1	–	–	0.02	–	–	-0.01
APC2	–	–	-2.51*	–	–	-2.60*

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.19(a): CORPUS UTERI (ICD-10 : C54) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

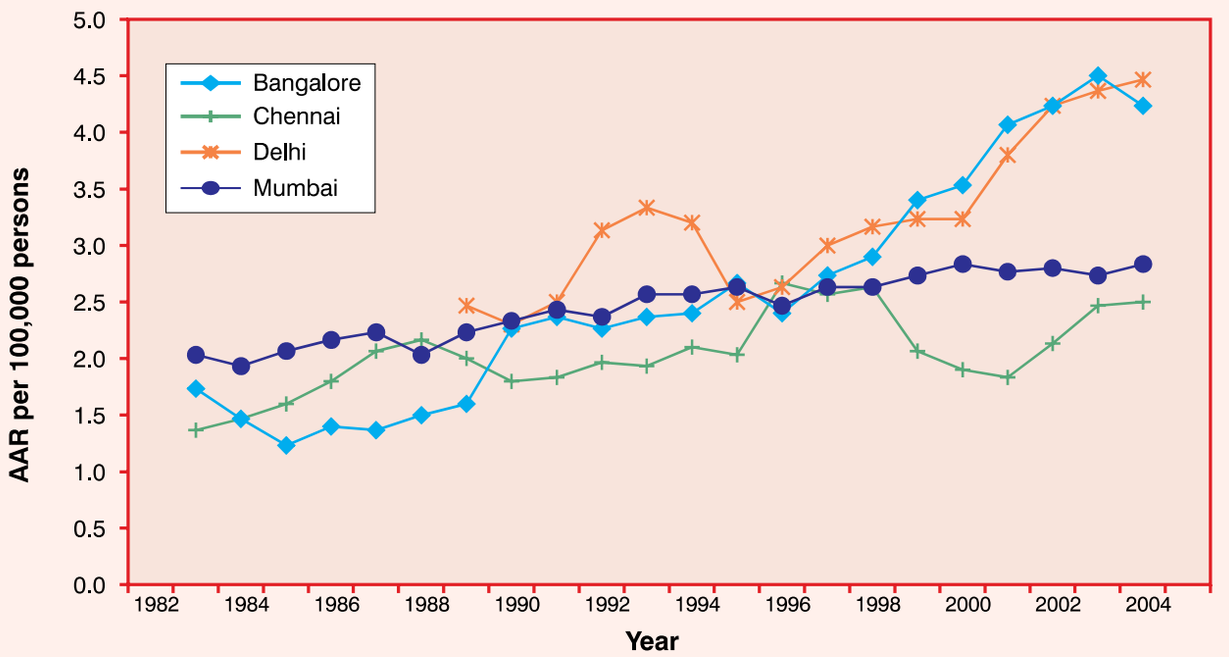


Table 4.19(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	1.7	1.3		2.1
1983	2.1	1.0		2.1
1984	1.4	1.8		1.9
1985	0.9	1.6		1.8
1986	1.4	1.4		2.5
1987	1.9	2.4		2.2
1988	0.8	2.4	2.6	2.0
1989	1.8	1.7	2.4	1.9
1990	2.2	1.9	2.4	2.8
1991	2.8	1.8	2.1	2.3
1992	2.1	1.8	3.0	2.2
1993	1.9	2.3	4.3	2.6
1994	3.1	1.7	2.7	2.9
1995	2.2	2.3	2.6	2.2
1996	2.7	2.1	2.2	2.8
1997	2.3	3.6	3.1	2.4
1998	3.2	2.0	3.7	2.7
1999	3.2	2.3	2.7	2.8
2000	3.8	1.9	3.3	2.7
2001	3.6	1.5	3.7	3.0
2002	4.8	2.1	4.4	2.6
2003	4.3	2.8	4.6	2.8
2004	4.4	2.5	4.1	2.8
2005	4.0	2.2	4.7	2.9
Slope	**0.140**	**0.039**	**0.124**	**0.041**
p-value	**0.001**	**0.010**	**0.001**	**0.001**

Fig. 4.19(b): CORPUS UTERI (ICD-10 : C54) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

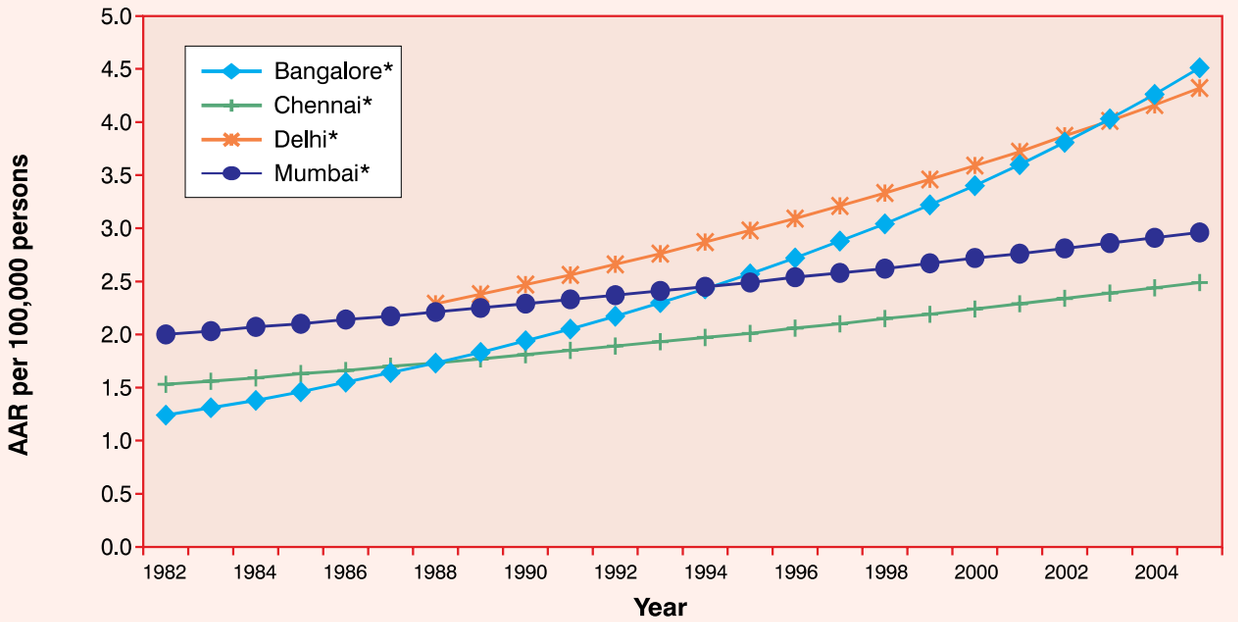


Table 4.19(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*
1982	1.2	1.5		2
1983	1.3	1.6		2.0
1984	1.4	1.6		2.1
1985	1.5	1.6		2.1
1986	1.6	1.7		2.1
1987	1.6	1.7		2.2
1988	1.7	1.7	2.3	2.2
1989	1.8	1.8	2.4	2.3
1990	1.9	1.8	2.5	2.3
1991	2.1	1.9	2.6	2.3
1992	2.2	1.9	2.7	2.4
1993	2.3	1.9	2.8	2.4
1994	2.4	2.0	2.9	2.5
1995	2.6	2.0	3.0	2.5
1996	2.7	2.1	3.1	2.5
1997	2.9	2.1	3.2	2.6
1998	3.0	2.2	3.3	2.6
1999	3.2	2.2	3.5	2.7
2000	3.4	2.2	3.6	2.7
2001	3.6	2.3	3.7	2.8
2002	3.8	2.3	3.9	2.8
2003	4.0	2.4	4.0	2.9
2004	4.3	2.4	4.2	2.9
2005	4.5	2.5	4.3	3.0
APC0	5.79*	2.15*	3.80*	1.73*
APC1	–	–	–	–
APC2	–	–	–	–

Values of years where a shift in trend observed is highlighted; represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.20(a): OVARY (ICD-10 : C56) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

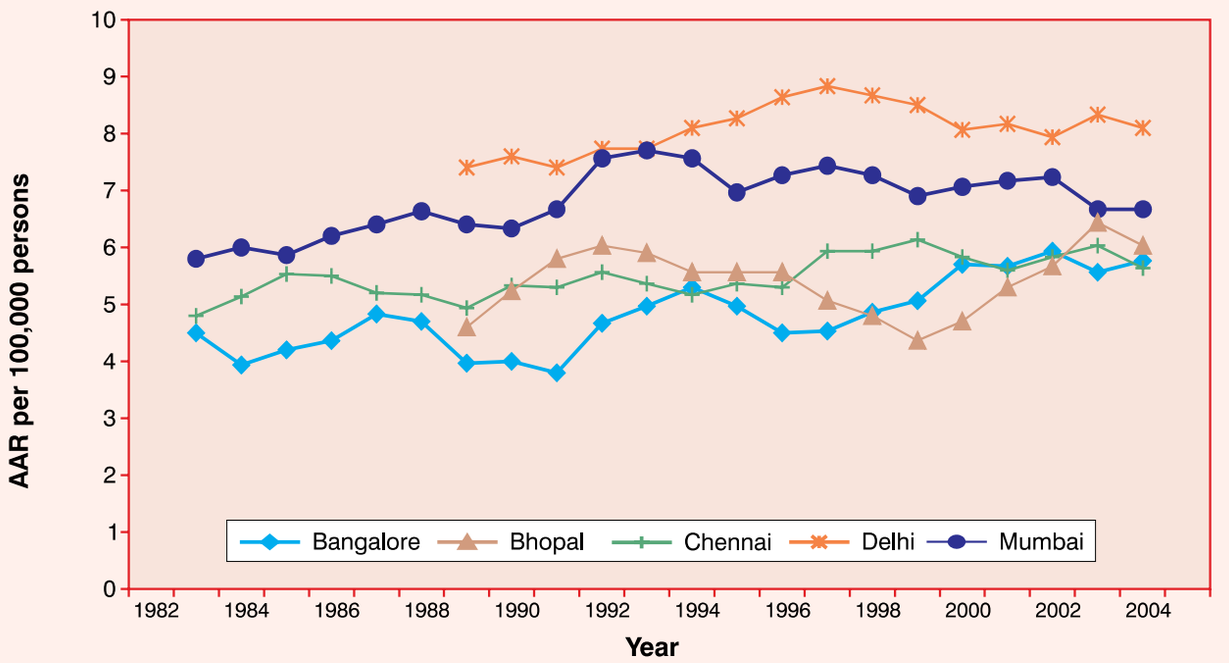


Table 4.20(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	4.6		4.2		5.6
1983	3.9		4.4		6
1984	5.0		5.8		5.8
1985	2.9		5.2		6.2
1986	4.7		5.6		5.6
1987	5.5		5.7		6.8
1988	4.3	3.7	4.3	7.3	6.8
1989	4.3	5.5	5.5	8.0	6.3
1990	3.3	4.6	5.0	6.9	6.1
1991	4.4	5.6	5.5	7.9	6.6
1992	3.7	7.2	5.4	7.4	7.3
1993	5.9	5.3	5.8	7.9	8.8
1994	5.3	5.2	4.9	7.9	7.0
1995	4.7	6.2	4.8	8.5	6.9
1996	4.9	5.3	6.4	8.4	7.0
1997	3.9	5.2	4.7	9.0	7.9
1998	4.8	4.7	6.7	9.1	7.4
1999	5.9	4.5	6.4	7.9	6.5
2000	4.5	3.9	5.3	8.5	6.8
2001	6.7	5.7	5.8	7.8	7.9
2002	5.8	6.3	5.7	8.2	6.8
2003	5.3	5.0	6.0	7.8	7.0
2004	5.6	8.0	6.4	9.0	6.2
2005	6.4	5.1	4.5	7.5	6.8
Slope	**0.079**	**0.044**	**0.040**	**0.046**	**0.051**
p-value	**0.003**	0.378	**0.049**	0.095	**0.019**

Fig. 4.20(b): OVARY (ICD-10 : C56) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

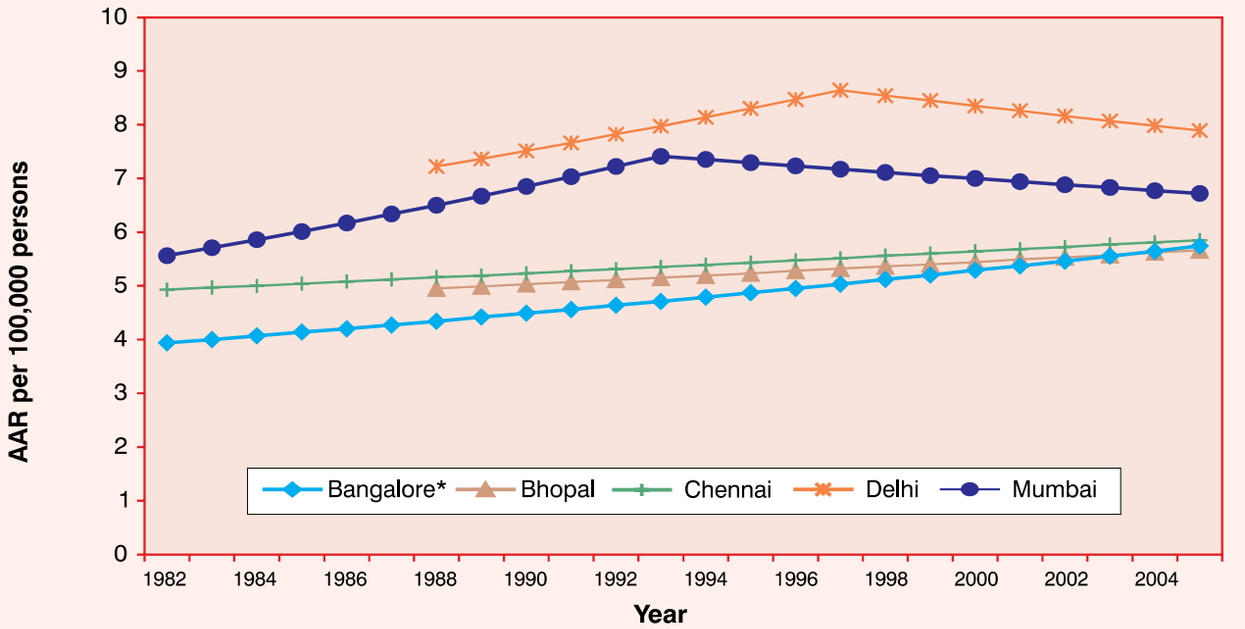


Table 4.20(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP1*	JP1*
1982	3.9		4.9		5.6
1983	4.0		5.0		5.7
1984	4.1		5.0		5.9
1985	4.1		5.0		6.0
1986	4.2		5.1		6.2
1987	4.3		5.1		6.3
1988	4.3	5.0	5.2	7.2	6.5
1989	4.4	5.0	5.2	7.4	6.7
1990	4.5	5.0	5.2	7.5	6.9
1991	4.6	5.1	5.3	7.7	7.0
1992	4.6	5.1	5.3	7.8	7.2
1993	4.7	5.2	5.4	8.0	7.4
1994	4.8	5.2	5.4	8.1	7.4
1995	4.9	5.2	5.4	8.3	7.3
1996	5.0	5.3	5.5	8.5	7.2
1997	5.0	5.3	5.5	8.6	7.2
1998	5.1	5.4	5.6	8.5	7.1
1999	5.2	5.4	5.6	8.5	7.1
2000	5.3	5.4	5.6	8.4	7.0
2001	5.4	5.5	5.7	8.3	6.9
2002	5.5	5.5	5.7	8.2	6.9
2003	5.6	5.6	5.8	8.1	6.8
2004	5.6	5.6	5.8	8.0	6.8
2005	5.7	5.7	5.9	8.0	6.7
APC0	1.65*	0.79	0.75	0.57	0.79*
APC1	–	–	–	2.02*	2.64*
APC2	–	–	–	-1.12	-0.81

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.21(a): PROSTATE (ICD-10 : C61) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

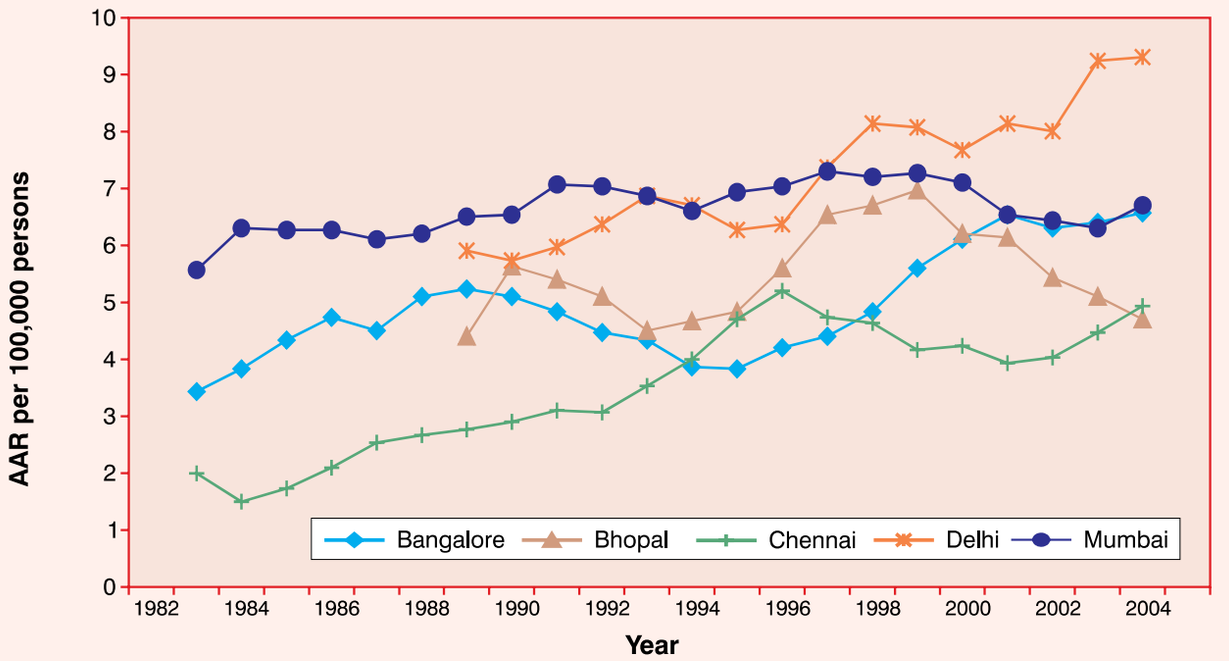


Table 4.21(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	3.7		2.8		5.1
1983	2.9		2.0		5.4
1984	3.7		1.2		6.2
1985	4.9		1.3		7.3
1986	4.4		2.7		5.3
1987	4.9		2.3		6.2
1988	4.2	1.9	2.6	6.3	6.8
1989	6.2	5.0	3.1	5.8	5.6
1990	5.3	6.3	2.6	5.6	7.1
1991	3.8	5.6	3.0	5.8	6.9
1992	5.4	4.3	3.7	6.5	7.2
1993	4.2	5.4	2.5	6.8	7.0
1994	3.4	3.8	4.4	7.3	6.4
1995	4.0	4.8	5.1	6.0	6.4
1996	4.1	5.9	4.6	5.5	8.0
1997	4.5	6.1	5.9	7.6	6.7
1998	4.6	7.6	3.7	9.0	7.2
1999	5.4	6.4	4.3	7.8	7.7
2000	6.8	6.9	4.5	7.4	6.9
2001	6.1	5.3	3.9	7.8	6.7
2002	6.7	6.2	3.4	9.2	6.0
2003	6.1	4.8	4.8	7.0	6.6
2004	6.4	4.3	5.2	11.5	6.3
2005	7.2	5.0	4.8	9.4	7.2
Slope(b)	**0.118**	**0.073**	**0.141**	**0.230**	**0.046**
p-value	**0.001**	0.221	**0.001**	**0.001**	**0.030**

Fig. 4.21(b): PROSTATE (ICD-10 : C61) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

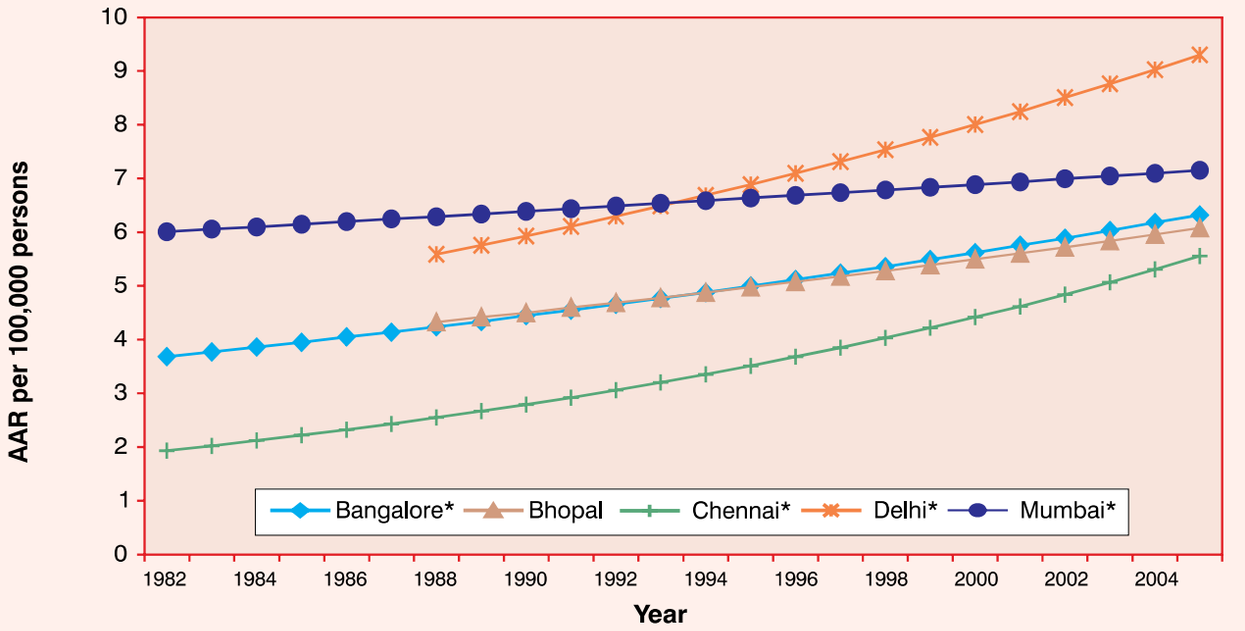


Table 4.21(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*	JP0*
1982	3.7		1.9		6.0
1983	3.8		2.0		6.1
1984	3.9		2.1		6.1
1985	3.9		2.2		6.1
1986	4.0		2.3		6.2
1987	4.1		2.4		6.2
1988	4.2	4.3	2.5	5.6	6.3
1989	4.3	4.4	2.7	5.8	6.3
1990	4.4	4.5	2.8	5.9	6.4
1991	4.5	4.6	2.9	6.1	6.4
1992	4.7	4.7	3.1	6.3	6.5
1993	4.8	4.8	3.2	6.5	6.5
1994	4.9	4.9	3.3	6.7	6.6
1995	5.0	5.0	3.5	6.9	6.6
1996	5.1	5.1	3.7	7.1	6.7
1997	5.2	5.2	3.8	7.3	6.7
1998	5.4	5.3	4.0	7.5	6.8
1999	5.5	5.4	4.2	7.8	6.8
2000	5.6	5.5	4.4	8.0	6.9
2001	5.8	5.6	4.6	8.2	6.9
2002	5.9	5.7	4.8	8.5	7.0
2003	6.0	5.8	5.1	8.8	7.0
2004	6.2	6.0	5.3	9.0	7.1
2005	6.3	6.1	5.6	9.3	7.2
APC0	2.38*	2.02	4.71*	3.05*	0.76*
APC1	–	–	–	–	–
APC2	–	–	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.22(a): BRAIN NERVOUS SYSTEM (ICD-10 : C70-72) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

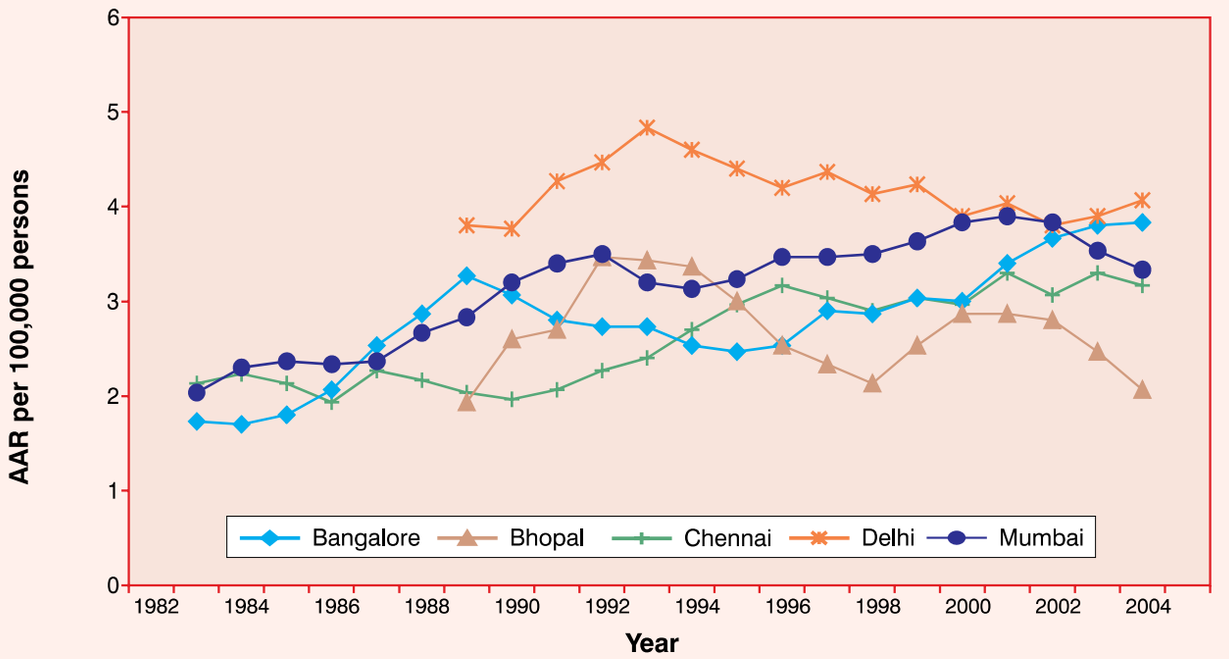


Table 4.22(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	1.6		1.2		1.8
1983	2.4		2.3		1.7
1984	1.0		2.9		2.6
1985	1.5		1.5		2.6
1986	2.7		2.0		1.9
1987	2.0		2.3		2.5
1988	2.9	0.9	2.5	3.8	2.7
1989	3.7	3.0	1.7	3.4	2.8
1990	3.2	1.9	1.9	4.2	3.0
1991	2.3	2.9	2.3	3.7	3.8
1992	2.9	3.3	2.0	4.9	3.4
1993	3.0	4.2	2.5	4.8	3.3
1994	2.3	2.8	2.7	4.8	2.9
1995	2.3	3.1	2.9	4.2	3.2
1996	2.8	3.1	3.3	4.2	3.6
1997	2.5	1.4	3.3	4.2	3.6
1998	3.4	2.5	2.5	4.7	3.2
1999	2.7	2.5	2.9	3.5	3.7
2000	3.0	2.6	3.7	4.5	4.0
2001	3.3	3.5	2.3	3.7	3.8
2002	3.9	2.5	3.9	3.9	3.9
2003	3.8	2.4	3.0	3.8	3.8
2004	3.7	2.5	3.0	4.0	2.9
2005	4.0	1.3	3.5	4.4	3.3
Slope(b)	**0.081**	**-0.012**	**0.069**	**-0.001**	**0.074**
p-value	**0.001**	0.764	**0.001**	0.969	**0.001**

Fig. 4.22(b): BRAIN, NERVOUS SYSTEM (ICD-10 : C70-72) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

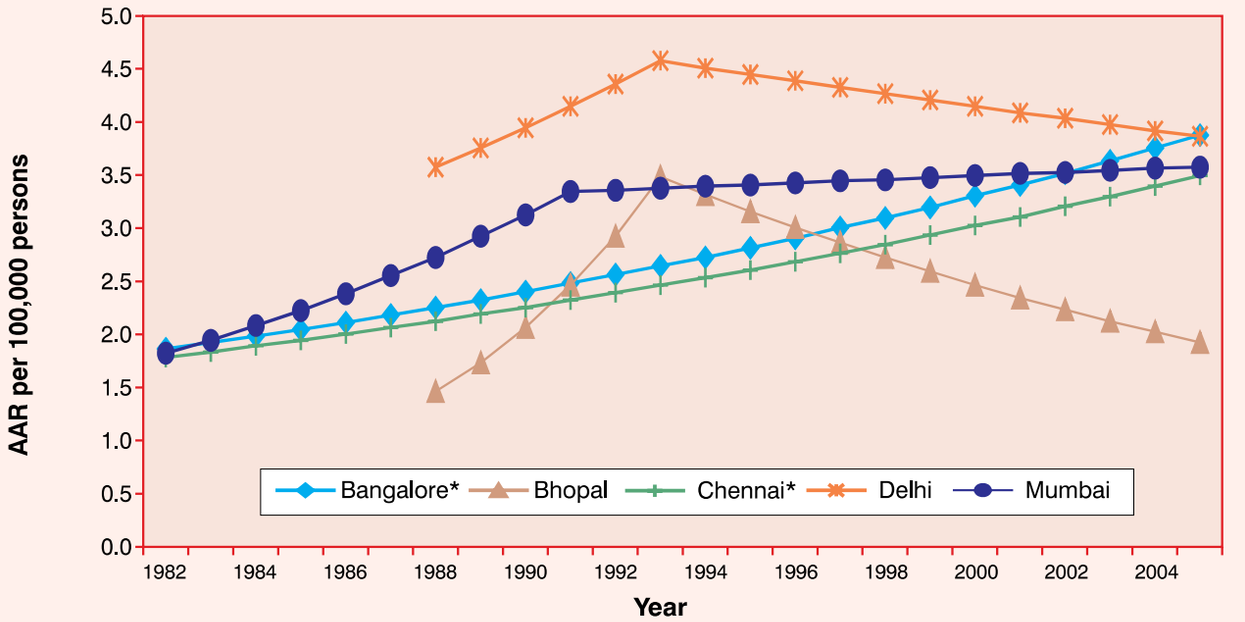


Table 4.22(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	**JP1***	**JP0***	**JP1***	**JP1***
1982	1.9		1.8		1.8
1983	1.9		1.8		1.9
1984	2.0		1.9		2.1
1985	2.0		1.9		2.2
1986	2.1		2.0		2.4
1987	2.2		2.1		2.6
1988	2.3	1.5	2.1	3.6	2.7
1989	2.3	1.7	2.2	3.8	2.9
1990	2.4	2.1	2.3	3.9	3.1
1991	2.5	2.5	2.3	4.1	**3.3**
1992	2.6	2.9	2.4	4.4	3.4
1993	2.6	**3.5**	2.5	**4.6**	3.4
1994	2.7	3.3	2.5	4.5	3.4
1995	2.8	3.2	2.6	4.4	3.4
1996	2.9	3.0	2.7	4.4	3.4
1997	3.0	2.9	2.8	4.3	3.4
1998	3.1	2.7	2.8	4.3	3.5
1999	3.2	2.6	2.9	4.2	3.5
2000	3.3	2.5	3.0	4.1	3.5
2001	3.4	2.3	3.1	4.1	3.5
2002	3.5	2.2	3.2	4.0	3.5
2003	3.6	2.1	3.3	4.0	3.5
2004	3.8	2.0	3.4	3.9	3.6
2005	3.9	1.9	3.5	3.9	3.6
APC0	**3.24***	0.01	**2.97***	0.00	**2.69***
APC1	–	19.07	–	5.04	**6.99***
APC2	–	-4.84	–	-1.39	0.49

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.23(a): BRAIN NERVOUS SYSTEM (ICD-10 : C70-72) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

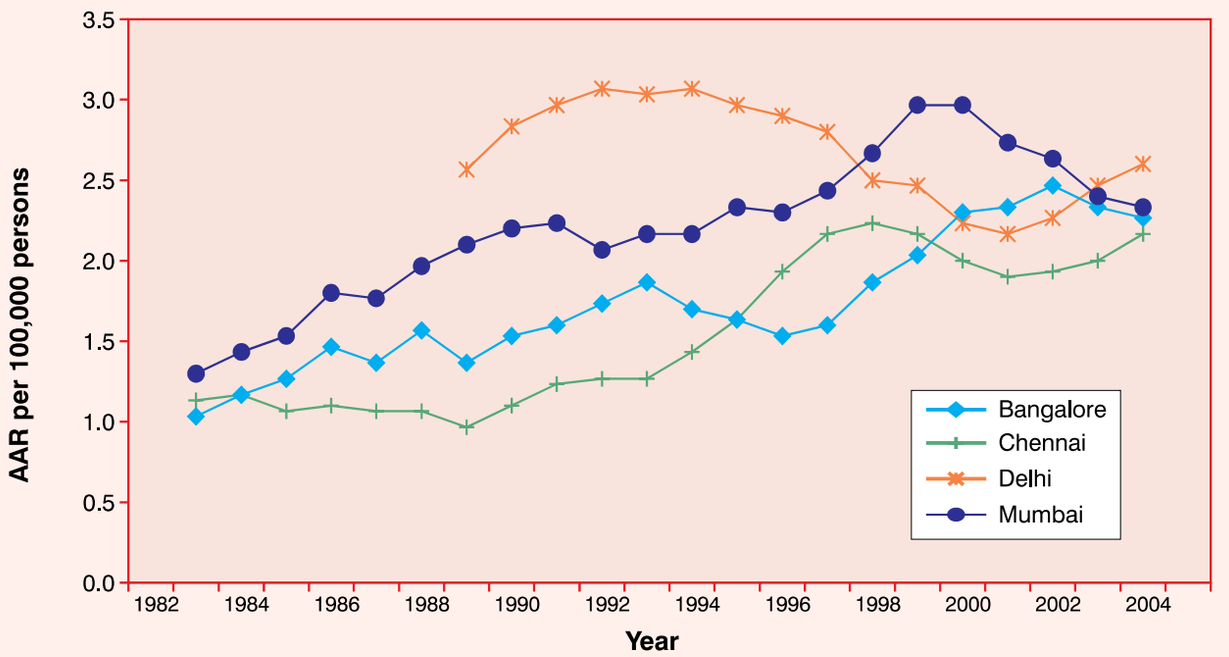


Table 4.23(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	1.1	0.8		1.3
1983	0.9	1.0		1.2
1984	1.1	1.6		1.4
1985	1.5	0.9		1.7
1986	1.2	0.7		1.5
1987	1.7	1.7		2.2
1988	1.2	0.8	2.0	1.6
1989	1.8	0.7	2.6	2.1
1990	1.1	1.4	3.1	2.6
1991	1.7	1.2	2.8	1.9
1992	2.0	1.1	3.0	2.2
1993	1.5	1.5	3.4	2.1
1994	2.1	1.2	2.7	2.2
1995	1.5	1.6	3.1	2.2
1996	1.3	2.1	3.1	2.6
1997	1.8	2.1	2.5	2.1
1998	1.7	2.3	2.8	2.6
1999	2.1	2.3	2.2	3.3
2000	2.3	1.9	2.4	3.0
2001	2.5	1.8	2.1	2.6
2002	2.2	2.0	2.0	2.6
2003	2.7	2.0	2.7	2.7
2004	2.1	2.0	2.7	1.9
2005	2.0	2.5	2.4	2.4
Slope	**0.054**	**0.063**	**-0.022**	**0.057**
p-value	**0.001**	**0.001**	0.229	**0.001**

Fig. 4.23(b): BRAIN NERVOUS SYSTEM (ICD-10 : C70-72) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

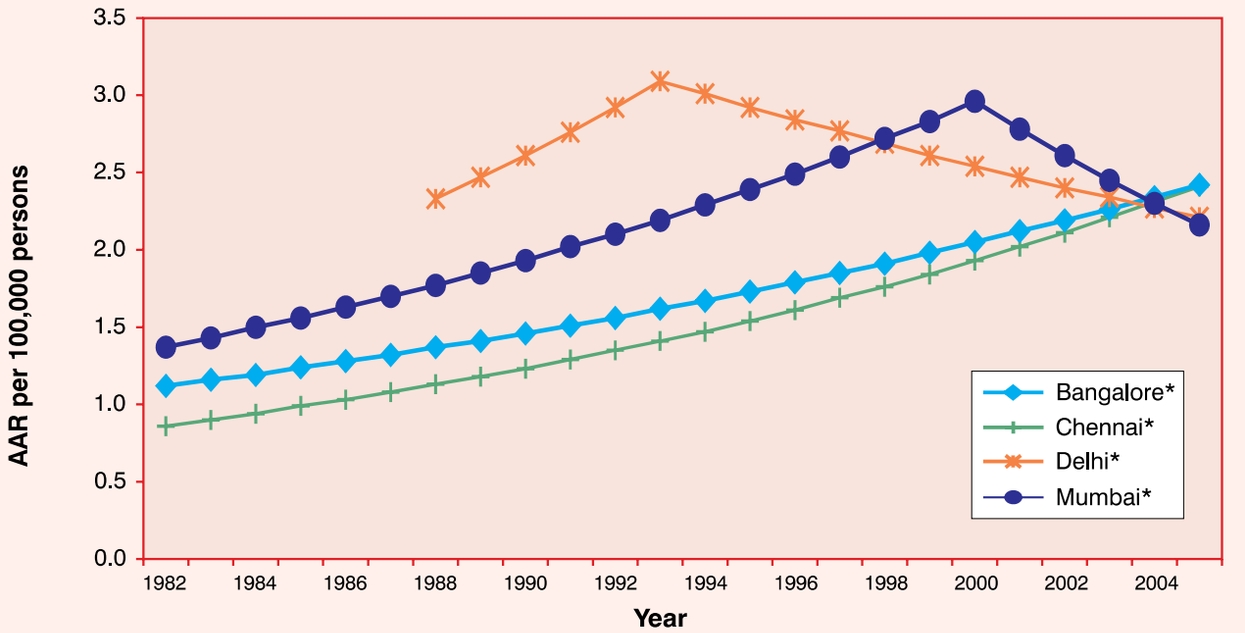


Table 4.23(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	**JP0***	**JP1***	**JP1***
1982	1.1	0.9		1.4
1983	1.2	0.9		1.4
1984	1.2	0.9		1.5
1985	1.2	1.0		1.6
1986	1.3	1.0		1.6
1987	1.3	1.1		1.7
1988	1.4	1.1	2.3	1.8
1989	1.4	1.2	2.5	1.9
1990	1.5	1.2	2.6	1.9
1991	1.5	1.3	2.8	2.0
1992	1.6	1.4	2.9	2.1
1993	1.6	1.4	**3.1**	2.2
1994	1.7	1.5	3.0	2.3
1995	1.7	1.5	2.9	2.4
1996	1.8	1.6	2.8	2.5
1997	1.9	1.7	2.8	2.6
1998	1.9	1.8	2.7	2.7
1999	2.0	1.8	2.6	2.8
2000	2.1	1.9	2.5	3.0
2001	2.1	2.0	2.5	2.8
2002	2.2	2.1	2.4	2.6
2003	2.3	2.2	2.3	2.5
2004	2.3	2.3	2.3	2.3
2005	2.4	2.4	2.2	2.2
APC0	**3.42***	**4.58***	-0.93	**2.90***
APC1	–	–	5.8	**4.35***
APC2	–	–	**-2.76***	-6.12

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.24(a): THYROID GLAND (ICD-10 : C73) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

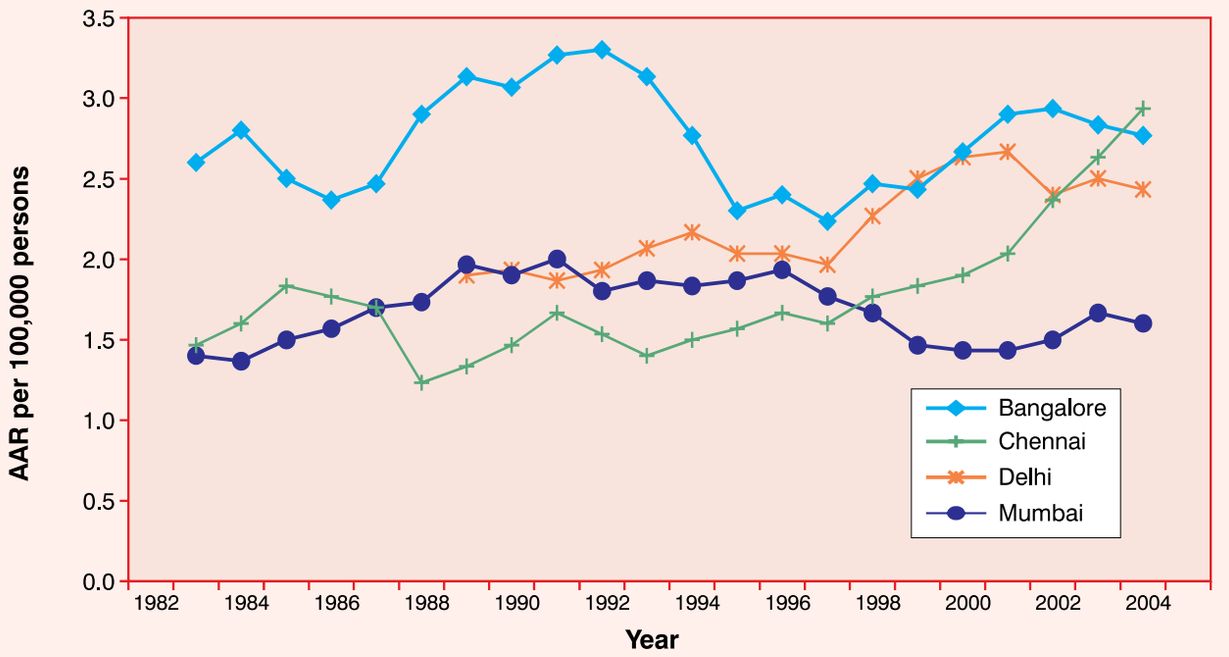


Table 4.24(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	2.2	1.3		1.5
1983	2.5	1.6		1.3
1984	3.1	1.5		1.4
1985	2.8	1.7		1.4
1986	1.6	2.3		1.7
1987	2.7	1.3		1.6
1988	3.1	1.5	1.7	1.8
1989	2.9	0.9	2.1	1.8
1990	3.4	1.6	1.9	2.3
1991	2.9	1.9	1.8	1.6
1992	3.5	1.5	1.9	2.1
1993	3.5	1.2	2.1	1.7
1994	2.4	1.5	2.2	1.8
1995	2.4	1.8	2.2	2.0
1996	2.1	1.4	1.7	1.8
1997	2.7	1.8	2.2	2.0
1998	1.9	1.6	2.0	1.5
1999	2.8	1.9	2.6	1.5
2000	2.6	2.0	2.9	1.4
2001	2.6	1.8	2.4	1.4
2002	3.5	2.3	2.7	1.5
2003	2.7	3.0	2.1	1.6
2004	2.3	2.6	2.7	1.9
2005	3.3	3.2	2.5	1.3
Slope	**0.005**	**0.050**	**0.049**	**0.000**
p-value	0.733	**0.001**	**0.001**	0.961

Fig. 4.24(b): THYROID GLAND (ICD-10 : C73) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

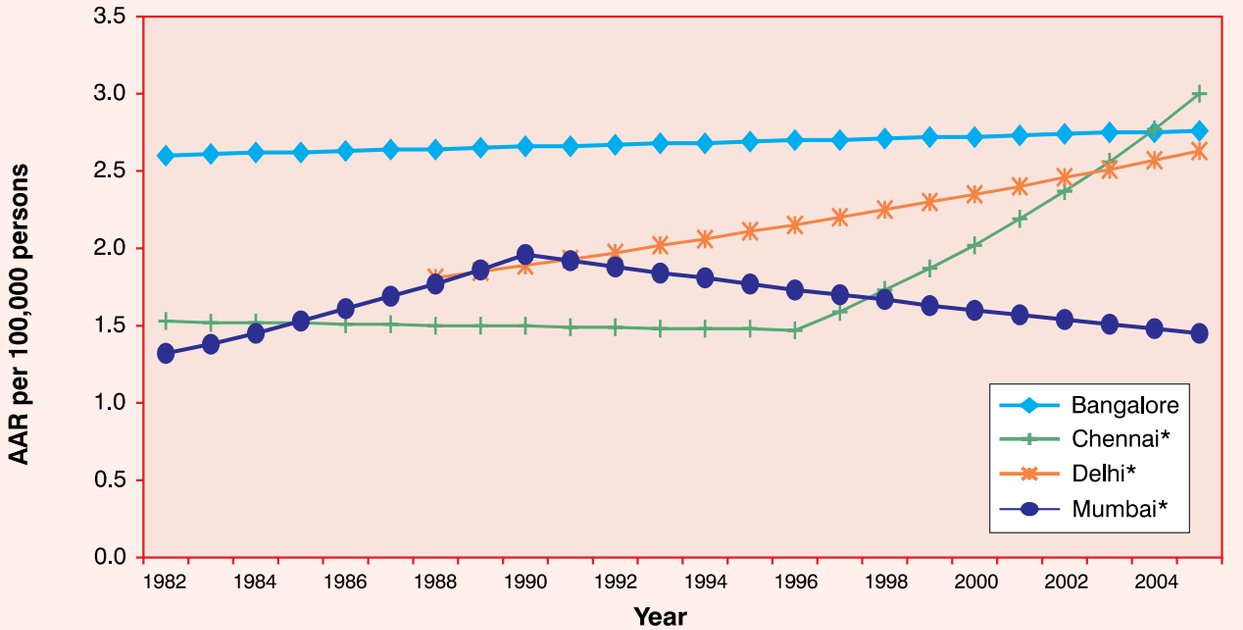


Table 4.24(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	**JP1***	**JP0***	**JP1***
1982	2.6	1.5		1.3
1983	2.6	1.5		1.4
1984	2.6	1.5		1.5
1985	2.6	1.5		1.5
1986	2.6	1.5		1.6
1987	2.6	1.5		1.7
1988	2.6	1.5	1.8	1.8
1989	2.7	1.5	1.9	1.9
1990	2.7	1.5	1.9	**2.0**
1991	2.7	**1.5**	1.9	1.9
1992	2.7	1.5	2.0	1.9
1993	2.7	1.5	2.0	1.8
1994	2.7	1.5	2.1	1.8
1995	2.7	1.5	2.1	1.8
1996	2.7	1.5	2.2	1.7
1997	2.7	1.6	2.2	1.7
1998	2.7	1.7	2.3	1.7
1999	2.7	1.9	2.3	1.6
2000	2.7	2.0	2.4	1.6
2001	2.7	2.2	2.4	1.6
2002	2.7	2.4	2.5	1.5
2003	2.8	2.6	2.5	1.5
2004	2.8	2.8	2.6	1.5
2005	2.8	3.0	2.6	1.5
APC0	0.26	**2.60***	**2.22***	-0.02
APC1	–	-0.26	–	**5.08***
APC2	**–**	**8.23***	**–**	**-2.00***

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.25(a): NHL (ICD-10 : C82-85,C96) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

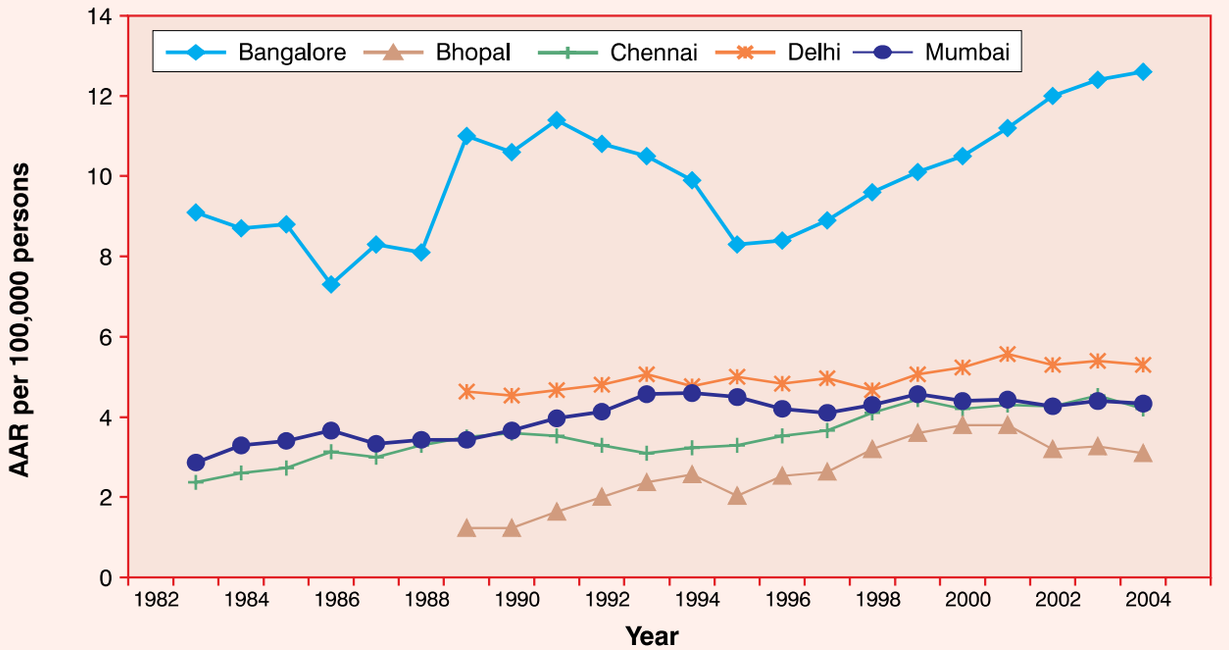


Table 4.25(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	3.1		2.7		2.5
1983	2.9		2.2		3
1984	3.1		2.2		3.1
1985	2.7		3.4		3.8
1986	3.0		2.6		3.3
1987	1.6		3.4		3.9
1988	3.7	1.0	3.0	4.8	2.8
1989	2.8	0.6	3.5	4.8	3.6
1990	4.5	2.1	4.0	4.3	3.9
1991	3.3	1.0	3.3	4.5	3.5
1992	3.6	1.8	3.3	5.2	4.5
1993	3.9	3.2	3.3	4.7	4.4
1994	3.0	2.1	2.7	5.3	4.8
1995	3.0	2.4	3.7	4.3	4.6
1996	2.3	1.6	3.5	5.4	4.1
1997	3.1	3.6	3.4	4.8	3.9
1998	3.5	2.7	4.1	4.7	4.3
1999	3.0	3.3	4.8	4.5	4.7
2000	3.6	4.8	4.4	6.0	4.7
2001	3.9	3.3	3.4	5.2	3.8
2002	3.7	3.3	5.1	5.5	4.8
2003	4.4	3.0	4.3	5.2	4.2
2004	4.3	3.5	4.2	5.5	4.2
2005	3.9	2.8	4.1	5.2	4.6
Slope(b)	**0.047**	**0.149**	**0.082**	**0.047**	**0.070**
p-value	**0.014**	**0.001**	**0.001**	**0.023**	**0.001**

Fig. 4.25(b): NHL (ICD-10 : C82-85,C96) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

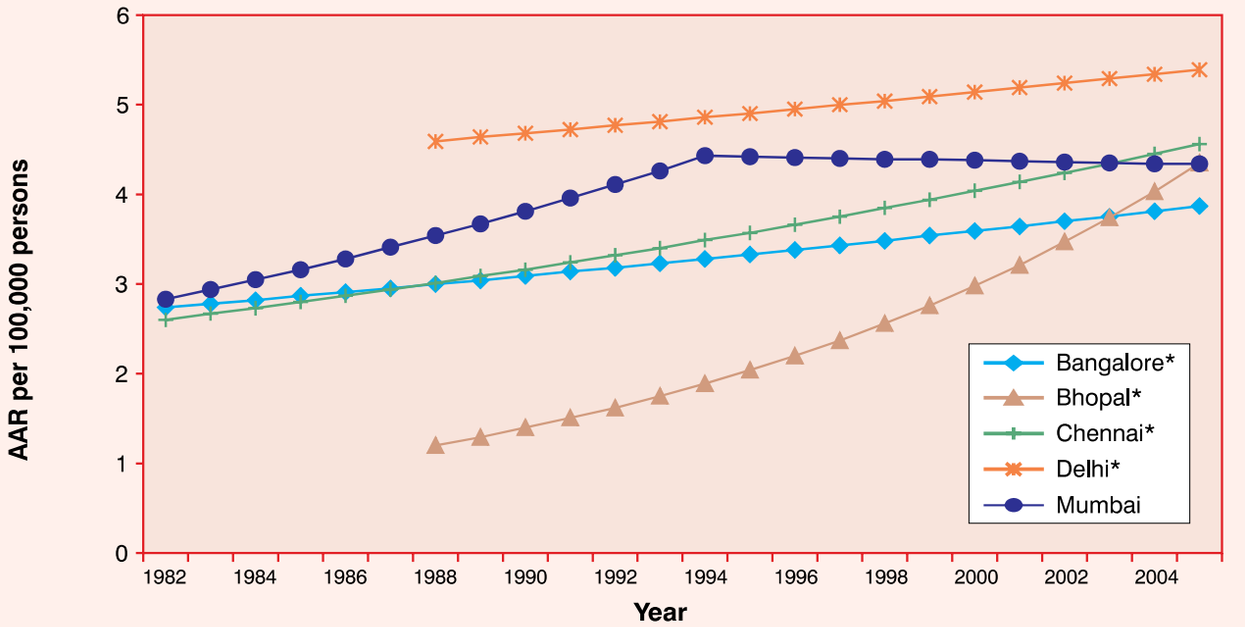


Table 4.25(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	**JP0***	**JP0***	**JP0***	**JP1***
1982	2.7		2.6		2.8
1983	2.8		2.7		2.9
1984	2.8		2.7		3.1
1985	2.9		2.8		3.2
1986	2.9		2.9		3.3
1987	3.0		2.9		3.4
1988	3.0	1.2	3.0	4.6	3.5
1989	3.0	1.3	3.1	4.6	3.7
1990	3.1	1.4	3.2	4.7	3.8
1991	3.1	1.5	3.2	4.7	4.0
1992	3.2	1.6	3.3	4.8	4.1
1993	3.2	1.8	3.4	4.8	4.3
1994	3.3	1.9	3.5	4.9	**4.4**
1995	3.3	2.0	3.6	4.9	4.4
1996	3.4	2.2	3.7	5.0	4.4
1997	3.4	2.4	3.8	5.0	4.4
1998	3.5	2.6	3.9	5.0	4.4
1999	3.5	2.8	3.9	5.1	4.4
2000	3.6	3.0	4.0	5.1	4.4
2001	3.6	3.2	4.1	5.2	4.4
2002	3.7	3.5	4.2	5.2	4.4
2003	3.8	3.7	4.3	5.3	4.4
2004	3.8	4.0	4.5	5.3	4.3
2005	3.9	4.4	4.6	5.4	4.3
APC0	**1.51***	**7.87***	**2.47***	**0.95***	**1.91***
APC1	–	–	–	–	**3.80***
APC2	–	–	–	–	-0.19

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.26(a): NHL (ICD-10 : C82-85,C96) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

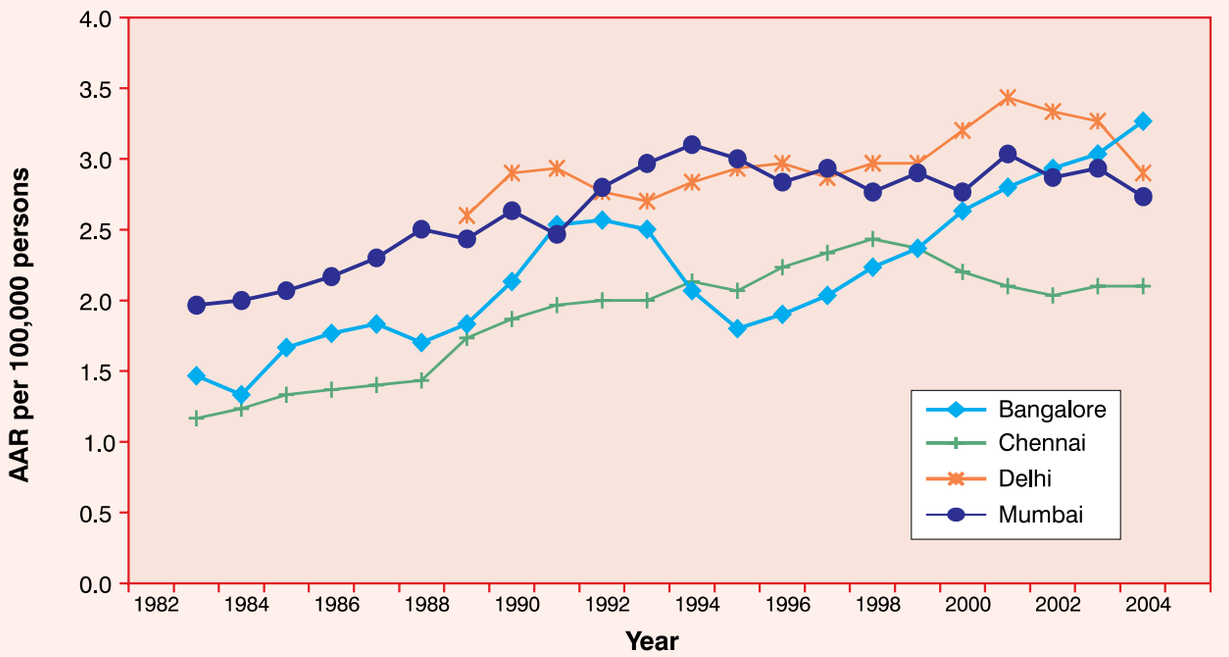


Table 4.26(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	1.4	1.3		1.8
1983	1.4	1.3		1.9
1984	1.6	0.9		2.2
1985	1.0	1.5		1.9
1986	2.4	1.6		2.1
1987	1.9	1.0		2.5
1988	1.2	1.6	2.3	2.3
1989	2.0	1.7	2.4	2.7
1990	2.3	1.9	3.1	2.3
1991	2.1	2.0	3.2	2.9
1992	3.2	2.0	2.5	2.2
1993	2.4	2.0	2.6	3.3
1994	1.9	2.0	3.0	3.4
1995	1.9	2.4	2.9	2.6
1996	1.6	1.8	2.9	3.0
1997	2.2	2.5	3.1	2.9
1998	2.3	2.7	2.6	2.9
1999	2.2	2.1	3.2	2.5
2000	2.6	2.3	3.1	3.3
2001	3.1	2.2	3.3	2.5
2002	2.7	1.8	3.9	3.3
2003	3.0	2.1	2.8	2.8
2004	3.4	2.4	3.1	2.7
2005	3.4	1.8	2.8	2.7
Slope	**0.075**	**0.048**	**0.034**	**0.043**
p-value	**0.001**	**0.001**	**0.044**	**0.001**

Fig. 4.26(b): NHL (ICD-10 : C82-85,C96) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

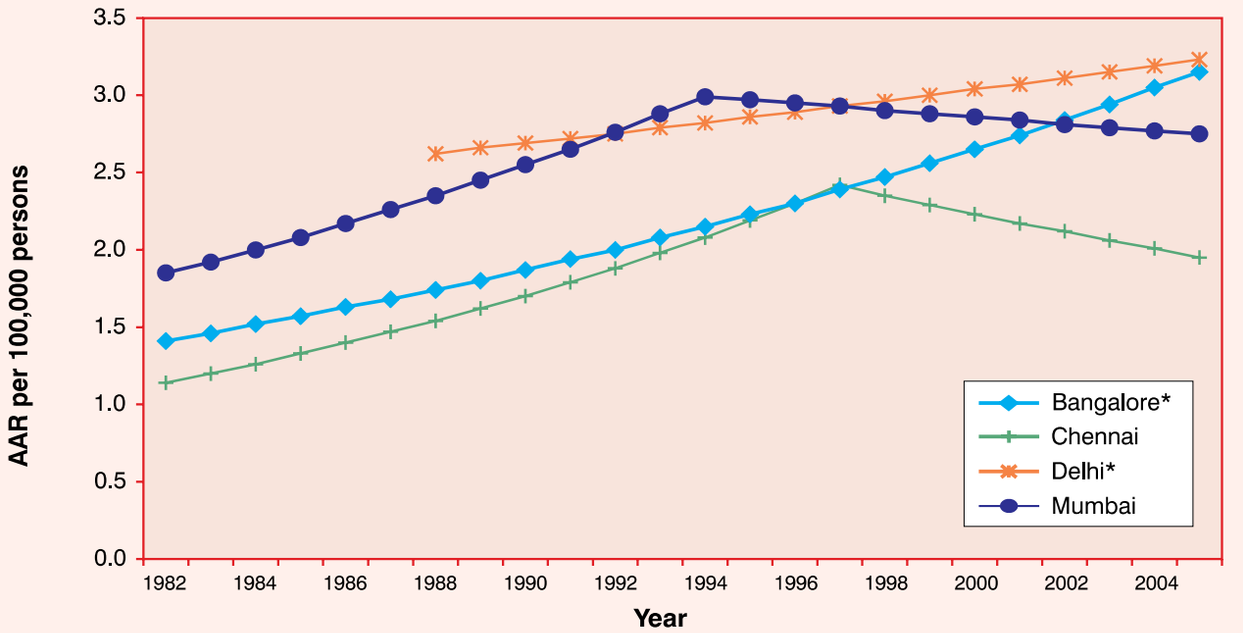


Table 4.26(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	**JP1***	**JP0***	**JP1***
1982	1.4	1.1		1.9
1983	1.5	1.2		1.9
1984	1.5	1.3		2.0
1985	1.6	1.3		2.1
1986	1.6	1.4		2.2
1987	1.7	1.5		2.3
1988	1.7	1.5	2.6	2.4
1989	1.8	1.6	2.7	2.5
1990	1.9	1.7	2.7	2.6
1991	1.9	1.8	2.7	2.7
1992	2.0	1.9	2.8	2.8
1993	2.1	2.0	2.8	2.9
1994	2.2	2.1	2.8	**3.0**
1995	2.2	2.2	2.9	3.0
1996	2.3	2.3	2.9	3.0
1997	2.4	**2.4**	2.9	2.9
1998	2.5	2.4	3.0	2.9
1999	2.6	2.3	3.0	2.9
2000	2.7	2.2	3.0	2.9
2001	2.7	2.2	3.1	2.8
2002	2.8	2.1	3.1	2.8
2003	2.9	2.1	3.2	2.8
2004	3.1	2.0	3.2	2.8
2005	3.2	2.0	3.2	2.8
APC0	**3.55***	**2.83***	**1.23***	**1.79***
APC1	**–**	**5.11***	**–**	**4.11***
APC2	–	-2.62	–	-0.78

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.27(a): LYMPHOID LEUKAEMIA (ICD-10 : C91) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

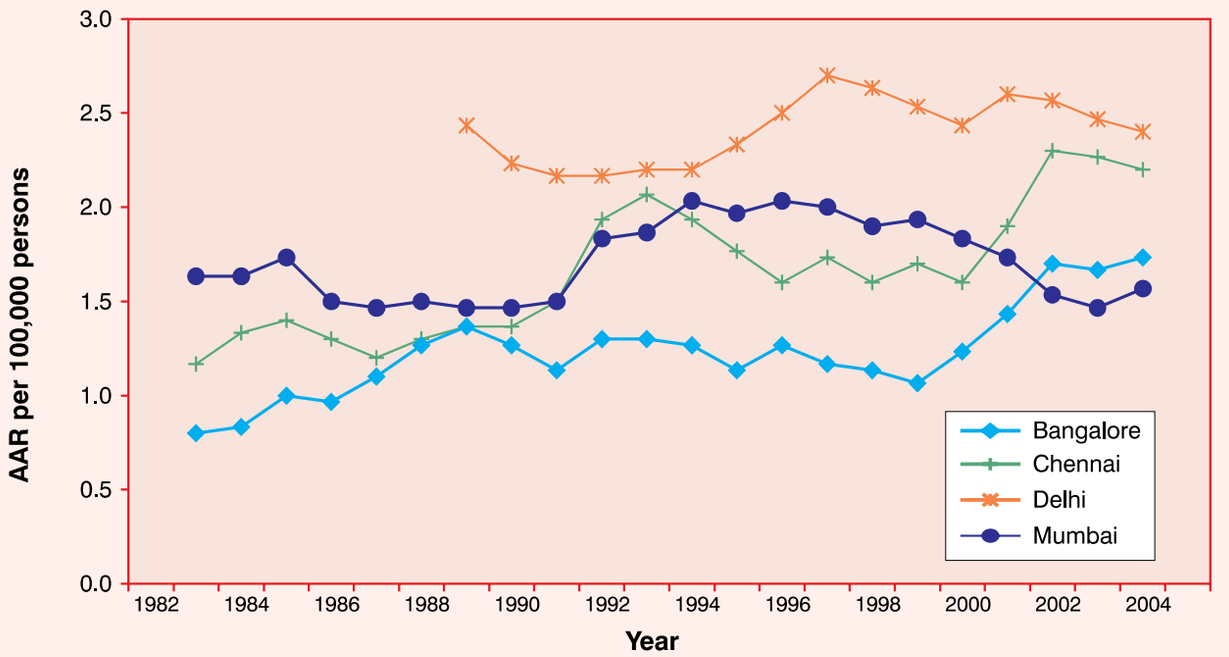


Table 4.27(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	0.8	1.2		1.7
1983	0.7	1.0		1.1
1984	0.9	1.3		2.1
1985	0.9	1.7		1.7
1986	1.2	1.2		1.4
1987	0.8	1.0		1.4
1988	1.3	1.4	2.8	1.6
1989	1.7	1.5	2.5	1.5
1990	1.1	1.2	1.9	1.3
1991	1.0	1.4	2.2	1.6
1992	1.3	1.9	2.3	1.6
1993	1.6	2.5	2.0	2.3
1994	1.0	1.8	2.3	1.7
1995	1.2	1.5	2.3	2.1
1996	1.2	2.0	2.4	2.1
1997	1.4	1.3	2.8	1.9
1998	0.9	1.9	2.9	2.0
1999	1.1	1.6	2.2	1.8
2000	1.2	1.6	2.5	2.0
2001	1.4	1.6	2.6	1.7
2002	1.7	2.5	2.7	1.5
2003	2.0	2.8	2.4	1.4
2004	1.3	1.5	2.3	1.5
2005	1.9	2.3	2.5	1.8
Slope(b)	**0.032**	**0.044**	**0.010**	**0.009**
p-value	**0.001**	**0.001**	0.451	0.316

Fig. 4.27(b): LYMPHOID LEUKAEMIA (ICD-10 : C91) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

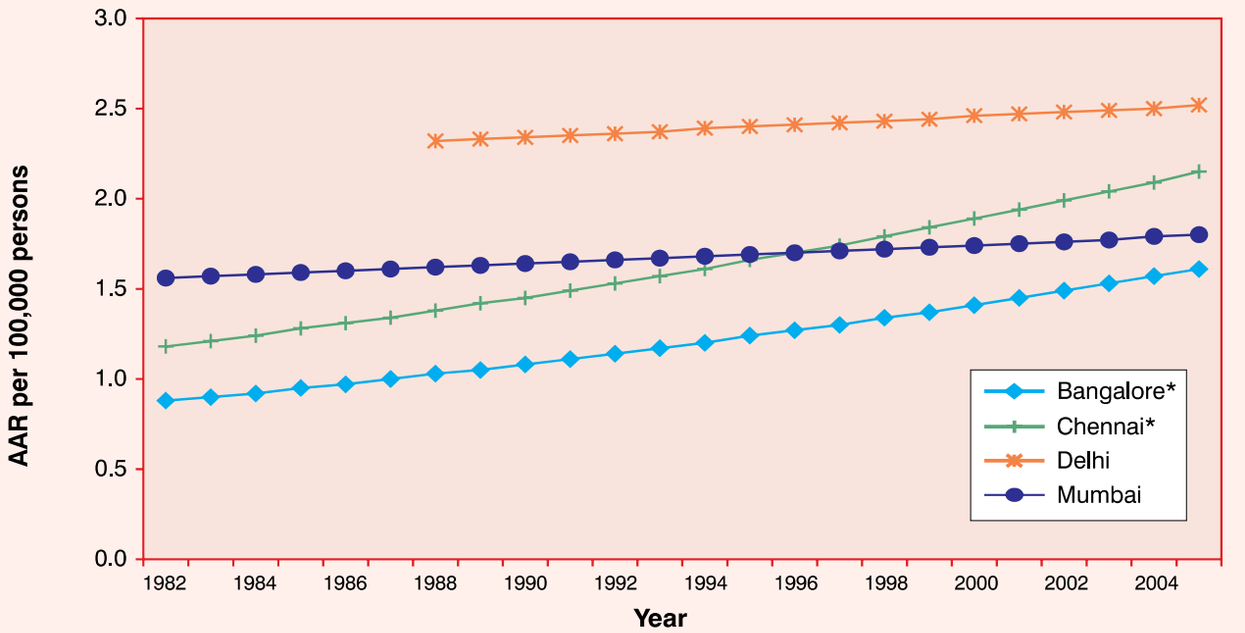


Table 4.27(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*
1982	0.9	1.2		1.6
1983	0.9	1.2		1.6
1984	0.9	1.2		1.6
1985	1.0	1.3		1.6
1986	1.0	1.3		1.6
1987	1.0	1.3		1.6
1988	1.0	1.4	2.3	1.6
1989	1.1	1.4	2.3	1.6
1990	1.1	1.5	2.3	1.6
1991	1.1	1.5	2.4	1.7
1992	1.1	1.5	2.4	1.7
1993	1.2	1.6	2.4	1.7
1994	1.2	1.6	2.4	1.7
1995	1.2	1.7	2.4	1.7
1996	1.3	1.7	2.4	1.7
1997	1.3	1.7	2.4	1.7
1998	1.3	1.8	2.4	1.7
1999	1.4	1.8	2.4	1.7
2000	1.4	1.9	2.5	1.7
2001	1.5	1.9	2.5	1.8
2002	1.5	2.0	2.5	1.8
2003	1.5	2.0	2.5	1.8
2004	1.6	2.1	2.5	1.8
2005	1.6	2.2	2.5	1.8
APC0	2.68*	2.64*	0.49	0.61
APC1	–	–	–	–
APC2	–	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.28(a): MYELOID LEUKAEMIA (ICD-10 : C92-94) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

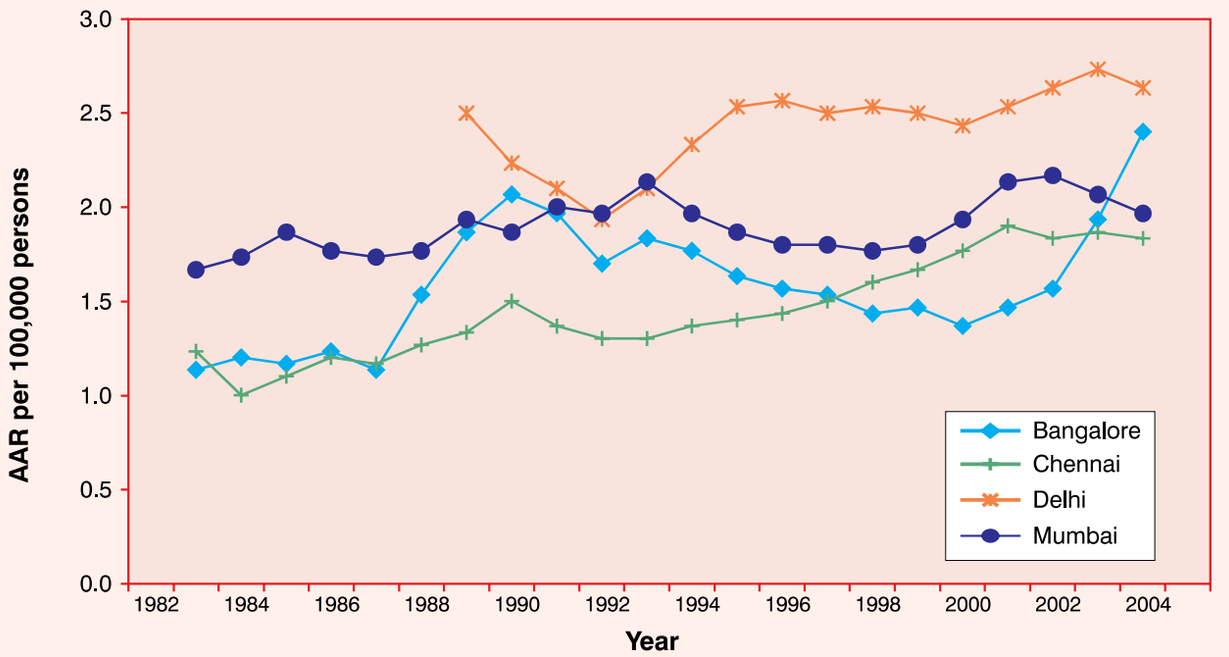


Table 4.28(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	1.0	1.7		1.6
1983	1.1	0.9		1.4
1984	1.3	1.1		2.0
1985	1.2	1.0		1.8
1986	1.0	1.2		1.8
1987	1.5	1.4		1.7
1988	0.9	0.9	2.8	1.7
1989	2.2	1.5	2.4	1.9
1990	2.5	1.6	2.3	2.2
1991	1.5	1.4	2.0	1.5
1992	1.9	1.1	2.0	2.3
1993	1.7	1.4	1.8	2.1
1994	1.9	1.4	2.5	2.0
1995	1.7	1.3	2.7	1.8
1996	1.3	1.5	2.4	1.8
1997	1.7	1.5	2.6	1.8
1998	1.6	1.5	2.5	1.8
1999	1.0	1.8	2.5	1.7
2000	1.8	1.7	2.5	1.9
2001	1.3	1.8	2.3	2.2
2002	1.3	2.2	2.8	2.3
2003	2.1	1.5	2.8	2.0
2004	2.4	1.9	2.6	1.9
2005	2.7	2.1	2.5	2.0
Slope(b)	**0.034**	**0.036**	**0.021**	**0.014**
p-value	**0.018**	**0.001**	0.107	**0.034**

Fig. 4.28(b): MYELOID LEUKAEMIA (ICD-10 : C92-94) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

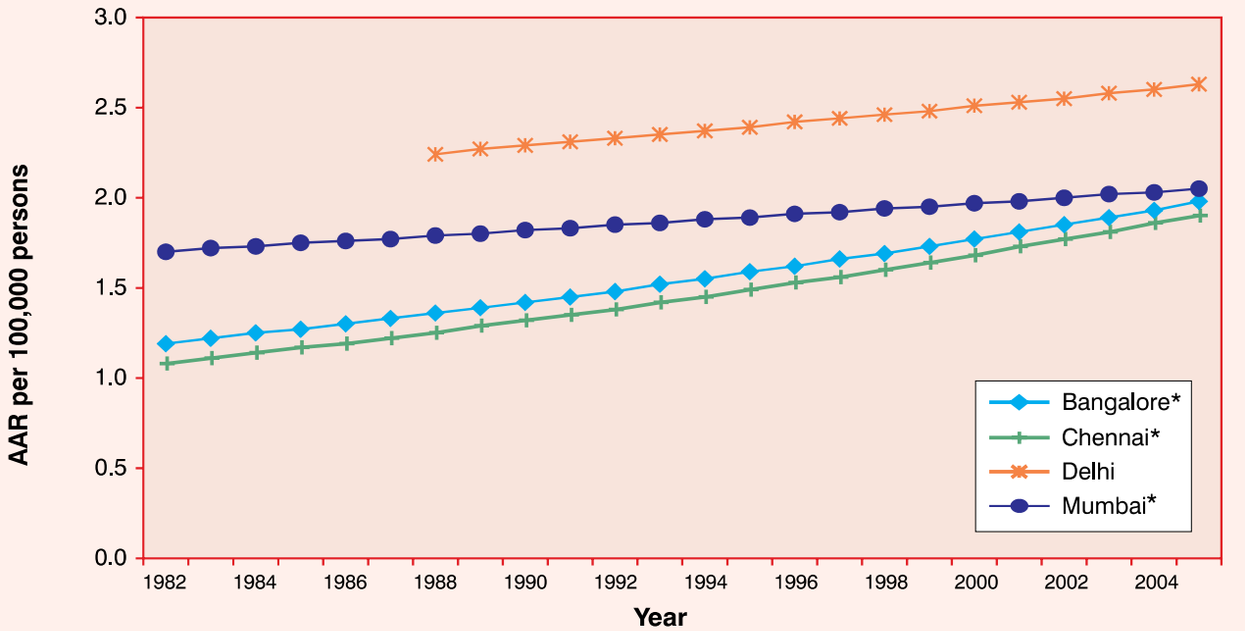


Table 4.28(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*
1982	1.2	1.1		1.7
1983	1.2	1.1		1.7
1984	1.3	1.1		1.7
1985	1.3	1.2		1.8
1986	1.3	1.2		1.8
1987	1.3	1.2		1.8
1988	1.4	1.3	2.2	1.8
1989	1.4	1.3	2.3	1.8
1990	1.4	1.3	2.3	1.8
1991	1.5	1.4	2.3	1.8
1992	1.5	1.4	2.3	1.9
1993	1.5	1.4	2.4	1.9
1994	1.6	1.5	2.4	1.9
1996	1.6	1.5	2.4	1.9
1997	1.7	1.6	2.4	1.9
1998	1.7	1.6	2.5	1.9
1999	1.7	1.6	2.5	1.9
2000	1.8	1.7	2.5	2.0
2001	1.8	1.7	2.5	2.0
2002	1.9	1.8	2.6	2.0
2003	1.9	1.8	2.6	2.0
2004	1.9	1.9	2.6	2.0
2005	2.0	1.9	2.6	2.1
APC0	2.23*	2.49*	0.93	0.80*
APC1	–	–	–	–
APC2	–	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.29(a): MYELOID LEUKAEMIA (ICD-10 : C92-94) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

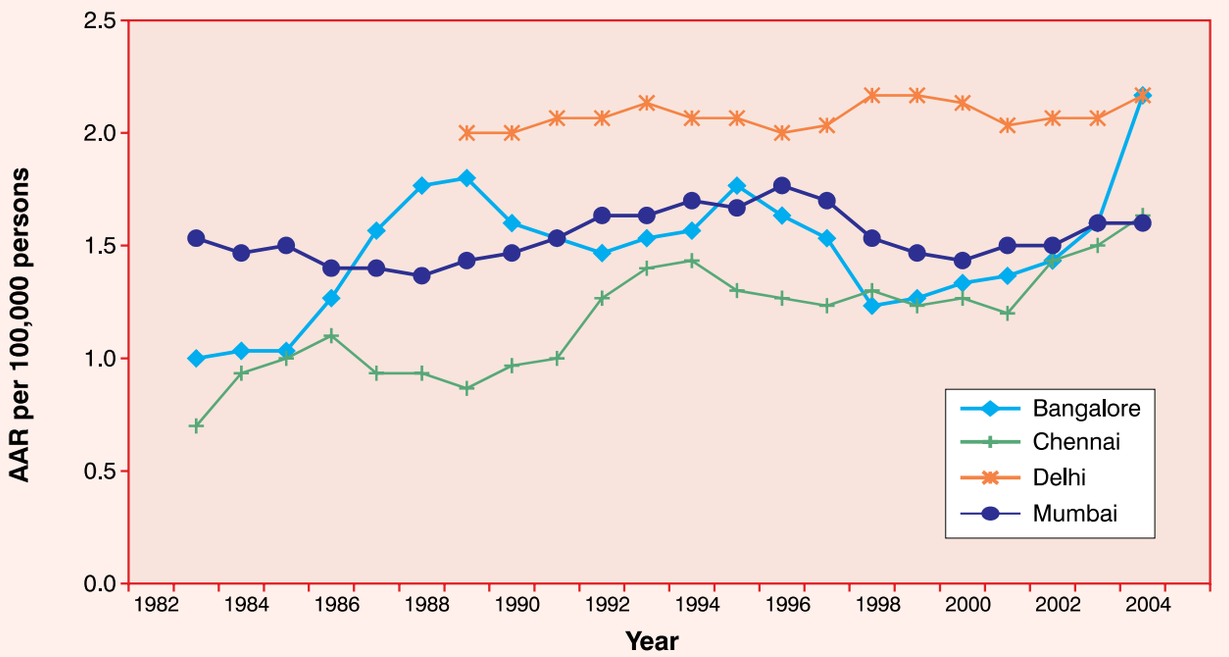


Table 4.29(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	1.0	0.4		1.6
1983	1.2	0.9		1.3
1984	0.8	0.8		1.7
1985	1.1	1.1		1.4
1986	1.2	1.1		1.4
1987	1.5	1.1		1.4
1988	2.0	0.6	2.0	1.4
1989	1.8	1.1	2.0	1.3
1990	1.6	0.9	1.4	1.6
1991	1.4	0.9	1.9	1.5
1992	1.6	1.2	2.2	1.5
1993	1.4	1.7	1.6	1.9
1994	1.6	1.3	2.2	1.5
1995	1.7	1.3	2.0	1.7
1996	2.0	1.3	1.9	1.8
1997	1.2	1.2	1.9	1.8
1998	1.4	1.2	2.1	1.5
1999	1.1	1.5	2.4	1.3
2000	1.3	1.0	1.8	1.6
2001	1.6	1.3	1.7	1.4
2002	1.2	1.3	2.1	1.5
2003	1.5	1.7	2.1	1.6
2004	2.1	1.5	1.7	1.7
2005	2.9	1.7	2.4	1.5
Slope	**0.030**	**0.035**	**0.012**	**0.005**
p-value	**0.020**	**0.001**	0.302	0.285

Fig. 4.29(b): MYELOID LEUKAEMIA (ICD-10 : C92-94) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

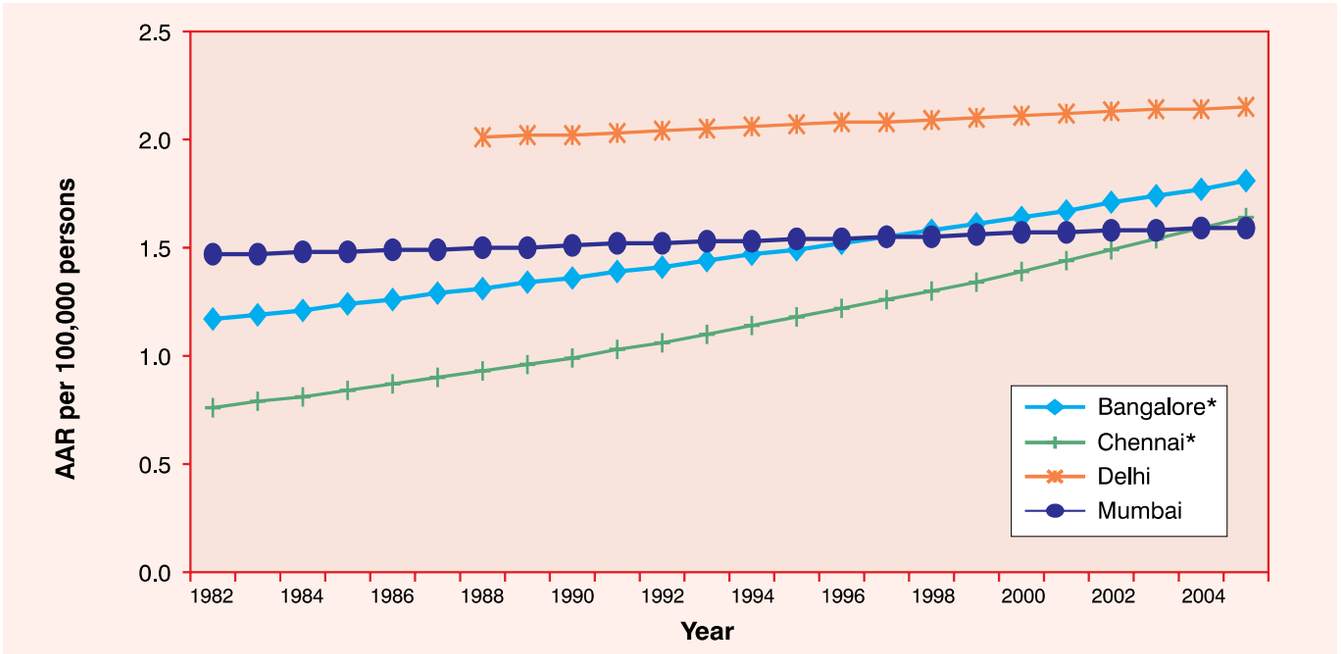


Table 4.29(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*
1982	1.2	0.8		1.5
1983	1.2	0.8		1.5
1984	1.2	0.8		1.5
1985	1.2	0.8		1.5
1986	1.3	0.9		1.5
1987	1.3	0.9		1.5
1988	1.3	0.9	2.0	1.5
1989	1.3	1.0	2.0	1.5
1990	1.4	1.0	2.0	1.5
1991	1.4	1.0	2.0	1.5
1992	1.4	1.1	2.0	1.5
1993	1.4	1.1	2.1	1.5
1994	1.5	1.1	2.1	1.5
1995	1.5	1.2	2.1	1.5
1996	1.5	1.2	2.1	1.5
1997	1.6	1.3	2.1	1.6
1998	1.6	1.3	2.1	1.6
1999	1.6	1.3	2.1	1.6
2000	1.6	1.4	2.1	1.6
2001	1.7	1.4	2.1	1.6
2002	1.7	1.5	2.1	1.6
2003	1.7	1.5	2.1	1.6
2004	1.8	1.6	2.1	1.6
2005	1.8	1.6	2.2	1.6
APC0	1.90*	3.41*	0.41	0.36
APC1	–	–	–	–
APC2	–	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Chapter 5

PROJECTION OF BURDEN OF CANCER

Projection of cancer burden means a systematic way of prediction of number of cancer cases for all anatomical sites or for a specific site and for a specified period of time. This could be based on time trend in incidence rates based on the projected population.

The present chapter projects the cancer cases for the country by sex for selected sites of cancer for the periods 2008-2010, 2015 & 2020 [Table 5(a) and 5(b)]. The incidence data generated by PBCRs at Bangalore, Barshi, Bhopal, Chennai, Delhi and Mumbai for the years 2001-2005 formed the sources of data. The Crude Incidence Rate (CR) was considered suitable for assessing the future load (magnitude) of cancer cases in the country. The CR is preferable to AAR as the latter is more suitable for comparison of rates between areas than for assessing the disease burden for the area. The combination of time trend in pooled crude rates of selected sites for past five years and population estimate by time was used to arrive at the projection for each of the above periods. The Linear Regression method was used to assess the time trend. For whichever sites the trend was not found to be significant, the latest rates were taken into consideration.

The pooled crude rates of the five urban registries (Bangalore, Bhopal, Chennai, Delhi and Mumbai) were taken to represent the estimates for all Indian states excluding states from the North East region. The Crude Rate of various cancer sites provided in the report of 2005-2006 for the North East region were assumed to represent the estimates for the same area. The crude rate of cancers of cervix and breast of the rural registry at Barshi was taken into account to represent the rural areas of India. Accordingly, the weightage of 0.7 and 0.3 for rural and urban areas respectively was used to estimate the projection for Breast and Cervix cancers.

The Percentage change observed in decadal growth rate of 1991-2001 as compared to the decadal growth of 1981-1991 was assumed to continue and correspondingly the growth rate of India is calculated separately for both males and females to calculate the yearly populations for the year 2001-2020.

Table 5(a): Projected Cases at India level for Selected Sites and Selected time periods (2008-2010, 2015, 2020) - MALES

ICD-10	Site Name	2008	2009	2010	2015	2020
C00-C96	**All Sites**	**447399**	**454842**	**462408**	**497081**	**534354**
C01-C02	**Tongue**	23932	24330	24735	26590	28584
C03-C06	**Mouth**	28066	29474	30921	38380	46785
C12-C13	**Hypopharynx**	14131	14366	14605	15700	16878
C15	**Oesophagus**	23573	23433	23281	22114	20642
C16	**Stomach**	24993	25408	25831	27768	29850
C18	**Colon**	11236	11423	11613	12484	13420
C19-C20	**Rectum**	11738	11933	12132	13041	14019
C22	**Liver**	14062	14295	14533	15623	16795
C23-C24	**Gall Bladder**	8396	8536	8678	9329	10028
C32	**Larynx**	24356	24761	25173	27060	29089
C33-C34	**Lung**	42863	43576	44301	47623	51194
C61	**Prostate**	25273	25693	26120	28079	30185
C70-C72	**Brain NS**	18238	18541	18850	20263	21782
C82-C95, C96	**NHL**	19835	20165	20501	22038	23690
C91	**Lymp. Leuk.**	9565	9724	9886	10627	11424
C92-C94	**Myeloid Leuk.**	11616	11809	12005	12905	13873

Table 5(b): Projected Cases at India level for Selected Sites and Selected time periods (2008-2010, 2015, 2020) - FEMALES

ICD-10	Site Name	2008	2009	2010	2015	2020
C00-C96	**All Sites**	**498773**	**507990**	**517378**	**563808**	**614404**
C01-C02	**Tongue**	7687	7829	7974	8689	9469
C03-C06	**Mouth**	14402	14669	14940	16280	17741
C12-C13	**Hypopharynx**	4620	4706	4793	5223	5691
C15	**Oesophagus**	17755	18083	18417	20070	21871
C16	**Stomach**	12458	12689	12923	14083	15347
C18	**Colon**	10675	11276	11896	15206	19014
C19-C20	**Rectum**	9005	9172	9341	10180	11093
C22	**Liver**	7564	7943	8334	10412	12795
C23-C24	**Gall Bladder**	17839	18169	18505	20166	21975
C32	**Larynx**	3894	3966	4039	4401	4796
C33-C34	**Lung**	13009	13250	13494	14705	16025
C50	**Breast**	84805	87693	90659	106124	123634
C53	**Cervix**	100088	101938	103821	113138	123291
C54	**Corpus Uteri**	14314	14579	14848	16181	17633
C56	**Ovary**	29386	29929	30482	33218	36199
C70-C72	**Brain NS**	11232	11440	11651	12697	13836
C73	**Thyroid Gland**	11329	11538	11751	12806	13955
C82-C85, C96	**NHL**	11696	11913	12133	13222	14408
C91	**Lymp. Leuk.**	5703	5808	5916	6447	7025
C92-C94	**Myeloid Leuk.**	11070	11770	12492	16363	20828

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Barshi (PBCR): Tata Memorial Centre Rural Cancer Project & Nargis Dutt Memorial Cancer Hospital, Barshi – 413 401 (Solapur), Maharashtra. *Email: barshiexp_registry@rediffmail.com*

Bhopal (PBCR): Department of Pathology, Gandhi Medical College, Bhopal – 462 001. *Email: pbcr_bhopal@yahoo.in*

Chennai (PBCR & HBCR): Cancer Institute (WIA), Annexe, 18, Sardar Patel Road, Chennai - 600 020. *Email: cancer_institute_wia@vsnl.com, iarcsurvival@yahoo.co.uk*

Delhi (PBCR): Institute of Rotary Cancer Hospital, Department of Pathology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi – 110 029. *Email: btyagi51@yahoo.co.in*

Mumbai (PBCR): Indian Cancer Society, 74, Jerbai Wadia Road, Parel, P.O. Box No. 6033, Mumbai – 400012. *Email: bcrics@vsnl.com; Website: http://www.indiancancersociety.org/*

Mumbai (HBCR): Tata Memorial Hospital, Parel, Mumbai – 400 012. *Email: cancer_epid@rediffmail.com.*

Thiruvananthapuram (HBCR & PBCR): Regional Cancer Centre, Medical College Campus, Thiruvananthapuram – 695 011. *Email: rcctvm@md2.vsnl.net.in.*

Dibrugarh District (PBCR & HBCR): Assam Medical College, Dibrugarh – 786 002. (ASSAM). *Email: pbcr_dibrugarh@rediffmail.com*

Kamrup Urban District (PBCR): Dr. Bhubaneswar Borooah Cancer Institute, Guwahati - 781 016 (ASSAM). *Email: dr_j_sarma@rediffmail.com.*

Silchar Town (PBCR): Silchar Medical College, Silchar - 788 014 (ASSAM). *Email: pbcrsmc@rediffmail.com, pbcrsmc@indiatimes.com.*

Imphal west District (PBCR): Regional Institute of Medical Sciences, Imphal - 795 004 (MANIPUR). *Email: pathlabs@yahoo.com.*

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Pune, Nagpur & Aurangabad (PBCR): Indian Cancer Society, 74, Jerbai Wadia Road, Parel, P.O. Box No. 6033, Mumbai – 400 012. *Email: bcrics@vsnl.com; Website: http://www.indiancancersociety.org/*

Kollam: Natural Background Radiation Cancer Registry, Karunagappally, Puthenthura P.O., Neendakara, Kollam - 691 588 (Kerala). *Email: nbrrkply@gmail.com*

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2. Annual Report 1983: National Cancer Registry, Indian Council of Medical Research, New Delhi, 1986
3. Annual Report 1984: National Cancer Registry, Indian Council of Medical Research, New Delhi, 1987
4. Annual Report 1985: National Cancer Registry, Indian Council of Medical Research, New Delhi, 1988
5. Annual Report 1986: National Cancer Registry, Indian Council of Medical Research, New Delhi, 1989
6. Annual Report 1987: National Cancer Registry Programme, Indian Council of Medical Research, New Delhi, 1989
7. Biennial Report 1988-1989: National Cancer Registry Programme, Indian Council of Medical Research, New Delhi, 1992
8. Consolidated Report of the Population Based Cancer Registries 1990-1996: National Cancer Registry Programme (ICMR), Bangalore, 2001
9. Consolidated Report of the Population Based Cancer Registries 1990-1996 Supplement: Year-wise Tabulation of Incident Cancers and Rates by Site and Gender: National Cancer Registry Programme (ICMR), Bangalore, 2001
10. Ten Year Consolidated Report of the Hospital Based Cancer Registries 1984-93: National Cancer Registry Programme (ICMR), Bangalore, 2001
11. NCRP - An Overview 1981-2001: National Cancer Registry Programme (ICMR), Bangalore, 2001
12. Two-Year Report of the Population Based Cancer Registries 1997-1998: National Cancer Registry Programme (ICMR), Bangalore, 2002
13. Five Year Consolidated Report on Hospital Based Cancer Registries : 1994-1998: National Cancer Registry Programme (ICMR), Bangalore, 2002
14. Development of an Atlas of Cancer in India. First All India Report 2001-2002 vol. I and II. [www.canceratlasindia.org]: National Cancer Registry Programme (ICMR), Bangalore, 2004
15. An Overview - Development of an Atlas of Cancer in India. First All India Report 2001-2002 vol. I and II. [www.canceratlasindia.org]: National Cancer Registry Programme (ICMR), Bangalore, 2004
16. Two-Year Report of the Population Based Cancer Registries 1999-2000: National Cancer Registry Programme (ICMR), Bangalore, 2005
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18. First Report of the Population Based Cancer Registries under North Eastern Regional Cancer Registry 2003-2004: National Cancer Registry (ICMR), Bangalore, 2006
19. An Overview - First Report of the North-East Population Based Cancer Registries 2003-2004: National Cancer Registry Programme (ICMR), Bangalore 2006
20. Consolidated Report of Population Based Cancer Registries 2001-2004: National Cancer Registry Programme (ICMR), Bangalore 2006
21. Consolidated report of Hospital Based Cancer Registries 2001-2003:National Cancer Registry Programme (ICMR), Bangalore, 2007
22. Second Report of the North East Population Based Cancer Registries 2005-2006: National Cancer Registry Programme (ICMR), Bangalore, 2008
23. Two-Year Report of the Population Based Cancer Registries 2004-2005: National Cancer Registry Programme (ICMR), Bangalore 2008

Chapter 1

INTRODUCTION

A common question of interest is “Is Cancer on the Rise?”. Cancer is known to be a disease that increases in incidence with increasing age. Control of communicable diseases, has increased life expectancy and therefore exposed more of the population towards the development of cancer. The increase in population due to growth also contributes to the increase in the number of cancer cases. Improved literacy, greater consciousness about health in general and awareness about cancer in particular makes more and more people seek medical advice at an earlier stage. Availability of sophisticated and improved diagnostic techniques aid in detection of tumours that would have been missed at earlier times. The question is whether cancer is on the increase after accounting for these factors and whether that rise is statistically significant.

One measure of determining such an increase would be to examine the age adjusted incidence rates (AAR) over time. This may or may not take into account all of the factors mentioned above. Nonetheless, it would give some indication of the trends in the disease. Cancer being a chronic disease (and unlike infectious diseases) with generally a long latent period and a rather prolonged clinical phase, year to year variations are slight. Therefore, in assessing time trends in AAR, the normal practice in registries across the world is to look at five yearly rates over decades. This would give a more definitive indication of the course of the disease. Nonetheless, the data presented here gives a fair account of the direction in which the incidence rates of the leading sites of cancer are proceeding across the years. Based on this, the report also provides an estimate of the burden of specific sites of cancer for the next decade. Such estimates will greatly facilitate deciding on priorities and planning site specific cancer control activities.

Cancer of the Corpus Uteri showed an increase in incidence rates in the four metros. The Annual Percentage Change (APC) was 5.8 in Bangalore and 3.8 in Delhi.

The Annual percentage of increase in cancer prostate in Chennai was 4.7 and 3.1 in Delhi.

In Chennai and Bangalore both males and females showed an increase in brain tumours. The annual percentage change was highest in Chennai females with an APC of 4.6.

Chapter 2

MATERIALS AND METHODS

The numerator data of all registries has undergone a series of range and consistency checks each year and again before preparing this report. Clarifications were sought wherever required from the respective PBCRs and the data finalised thereafter.

The difference distribution method *(Takiar & Shobana, 2009)* for estimating the calendar year wise denominator population by five year age group has been used. This was based on the census data of 1981, 1991 and 2001.

In determining the significance of trends, the actual value of the AAR rate for each year has been used. The significance of time trend in each PBCR was assessed based on the methods and formula provided by Boyle and Parkin, 1991 in the chapter from the IARC publication on Cancer Registration. In addition, the Joinpoint Regression Program of the NCI of USA has been used *(Kim et al, 2001)*.

About Joinpoint Regression Program:

Joinpoint Regression Program, Version 3.0, is statistical software for the analysis of trends using Joinpoint models, that is, where several different regression lines are connected together at the "Joinpoints". Cancer trends reported in NCI publications are calculated using the Joinpoint Regression Program to analyze rates calculated by the SEER. The software takes trend data (e.g. cancer rates) and fits the simplest Joinpoint model that the data allow. The user supplies the minimum and maximum number of Joinpoints. The program starts with the minimum number of Joinpoint (e.g. 0 Joinpoint, which is a straight line) and tests whether more Joinpoints are statistically significant and must be added to the model (upto that maximum number). This enables the user to test that an apparent change in trend is statistically significant. The tests of significance use a Monte Carlo Permutation method. The models may incorporate estimated variation for each point (e.g. when the responses are age adjusted rates) or use a Poisson model of variation. In addition, the models may also be linear on the log of the response (e.g. for calculating annual percentage rate change). The software also allows viewing one graph for each Joinpoint model, from the model with the minimum number of Joinpoints to the model with the maximum number of Joinpoints (Kim et al, 2001). For the report purposes, one Joinpoint model wherever feasible has been fitted to the data. It may be pointed out that whenever a strong linear trend exists in the data the one Joinpoint model results will tally exactly with that of linear regression method.

This report is based on the data of six PBCRs – viz., Bangalore, Barshi, Bhopal, Chennai, Delhi and Mumbai. For the PBCRs at Bangalore, Mumbai and Chennai, the data available is from 1982. Accordingly, the trend in AAR over time is for the 24 year period from 1982 to 2005. The PBCRs at Barshi, Bhopal and Delhi commenced from 1988. Accordingly, the time trend is for the 18 year period from 1988 to 2005.

While depicting the results of specific anatomical sites of cancer in chapter 4, those sites with fewer than 10 cases for any given year have been excluded. This is mostly seen in the case of Barshi and Bhopal PBCRs and in sites of cancer other than the first five or six leading sites.

Among males, cancers of the prostate, colon, rectum and liver, have shown statistically significant increase in incidence. Cancer of the prostate is the leading site of cancer among males in most of the western countries as is cancer of the colon. Among females, cancers of the breast, corpus uteri and lung have shown a rise.

Both males and females have recorded rising incidence rates for cancers of the brain as well as in tumours of the lymphoid and haemopoetic system, especially non-Hodgkin's Lymphoma.

Three other sites of cancer that have shown an increase in incidence rates in women are ovary, thyroid and gallbladder.

Among males in Bangalore, during 1982–83, stomach was the leading site of cancer and it continues to be so twenty four years down the line. In females in Bangalore, cancer of the lung that did not appear among ten leading sites in 1982-83 is the tenth leading site during 2004-05.

In males in Bhopal, cancer of the lung and mouth were the first and third leading sites earlier and have become the first two leading sites in 2004-05.

In males in Chennai, stomach was the leading site of cancer during 1982-83 and this site has been replaced by lung in more recent years.

Chapter 3

INDIVIDUAL REGISTRY - LEADING SITE GRAPHS

The following bar graphs provide the comparison of the leading sites of cancer for the first two years of registry operation and the recent two years data. This will be 1982–83 and 2004–05 for the PBCRs at Bangalore, Mumbai and Chennai and 1988-89 and 2004-05 for the registries at Barshi, Bhopal and Delhi.

Bangalore (Figure 3.1(a) & 3.1(b)) :

Males: Among males, during 1982–83, stomach was the leading site of cancer and it continues to be so twenty four years down the line. Cancer of the prostate was the tenth leading site in the earlier years and is now the fourth leading site. Cancers of the brain and colon that were not, are now among ten leading sites in 2004–05.

Females: Among females, cancer of the breast has replaced cancer of the cervix as the leading site. Cancers of the corpus uteri and ovary have increased in their ranking. Cancer of the lung that did not appear among ten leading sites in 1982-83 is the tenth leading site during 2004-05.

Barshi (Figure 3.2(a) & 3.2(b)) :

Males*:* Cancers of the hypopharynx and oesophagus continue to be the first two leading sites among males in Barshi. Cancer of the brain has appeared among the leading sites of cancer as also non-Hodgkin's Lymphoma (NHL).

Females: Among females, cancer of the cervix uteri continues to be the leading site. Cancer of the lung has appeared as the fifth leading site during 2004-05.

The data from Barshi is in relatively small numbers because of the smaller geographic area covered. Therefore, caution needs to be observed in interpreting this data.

Bhopal (Figure 3.3(a) & 3.3(b)) :

Males: Cancer of the lung and mouth were the first and third leading sites earlier and have become the first two leading sites in 2004-05. Cancer of the prostate has increased in ranking. The new sites of cancer that have appeared among the ten leading sites during 2004-05 are non-Hodgkin's Lymphoma, liver and myeloid leukaemia.

Females: Among females, as in other urban registries, cancer of the breast has replaced cancer of the cervix as the leading site of cancer and cancer of the ovary has risen in rank as the third leading site.

Chennai (Figure 3.4(a) & 3.4(b)) :

Males: Stomach was the leading site of cancer during 1982-83 and this site has been replaced by lung in more recent years. Cancers of the prostate and rectum have appeared as the seventh and tenth leading site of cancer. These sites were not seen among ten leading sites during 1982-83.

Females: Among females, cancer of the breast has replaced cancer of the cervix as the first leading site of cancer. Cancer of the ovary which was the fifth leading site earlier has gone up in rank. Cancer of the lung with brain and corpus uteri have appeared as the eighth and ninth leading sites of cancer during 2004-05.

Delhi (Figure 3.5(a) & 3.5(b)) :

Males*:* Cancer of the lung was and is the leading site of cancer among males. Cancer of the prostate which was the eighth leading site during 1988-89 has become the second leading site during 2004-05.

Females: Cancer of the breast has replaced cancer of the cervix as the leading site. Cancer of the ovary and gall bladder continue to be the third and fourth leading sites. Cancer of the corpus-uteri which was the tenth leading site has become fifth leading site of cancer. Cancer of the lung was not among the ten leading sites during 1988-89 has become sixth leading site during 2004-05.

Mumbai (Figure 3.6(a) & 3.6(b)) :

Males: Cancer of the lung continues to be the leading site of cancer. Cancer of the prostate which was the eighth leading site has now become the third leading site of cancer. Cancer of the brain which was not among ten leading sites during 1982-83 has become the tenth leading site of cancer.

Females: Cancer of the breast continues to be the leading site of cancer for almost a quarter of a century. Cancers of the ovary, lung and corpus uteri have gone up in their ranking.

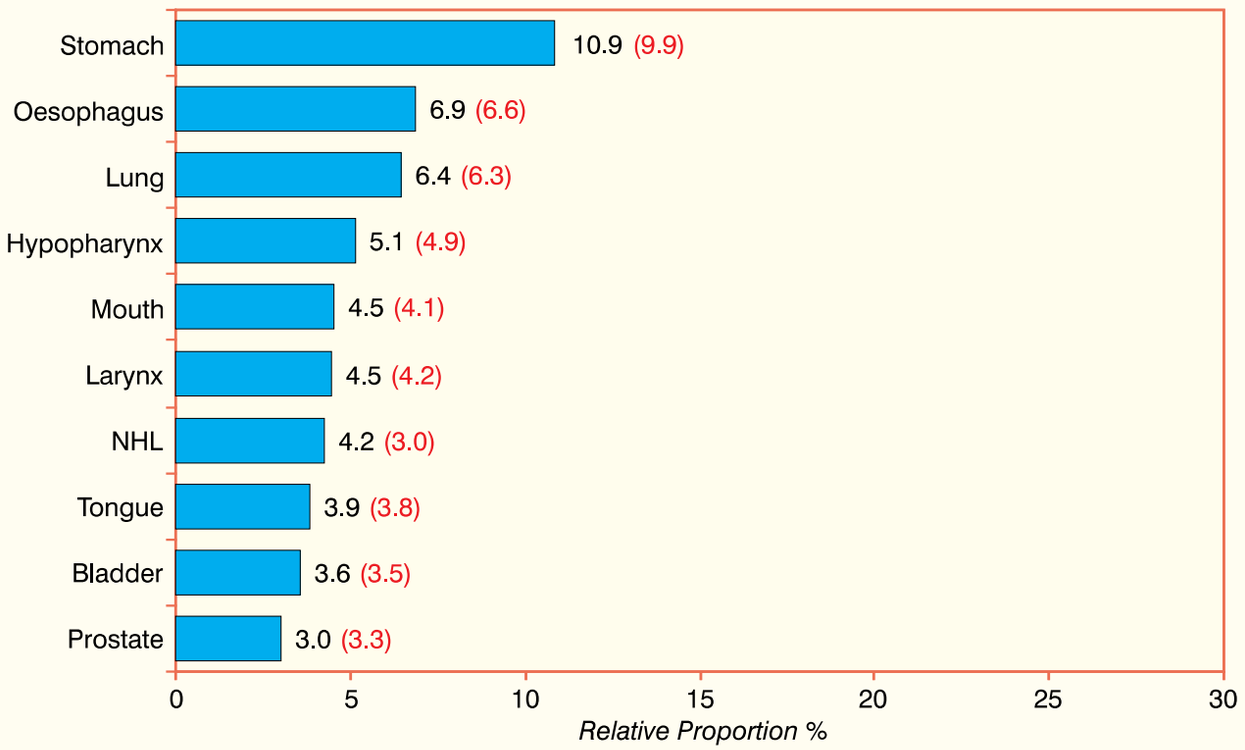
In males in Delhi, cancer of the prostate which was the eighth leading site during 1988-89 has become the second leading site during 2004-05. In females in Delhi, cancer of the breast has replaced cancer of the cervix as the leading site. Cancer of the ovary and gall bladder continue to be the third and fourth leading sites. Cancers of the corpus-uteri which was the tenth leading site has become fifth leading site of cancer. Cancer of the lung was not among the ten leading sites during 1988-89 has become sixth leading site during 2004-05.

In males in Mumbai, cancer of the prostate which was the eighth leading site has now become the third leading site of cancer.

Fig. 3.1(a): Ten Leading Sites of Cancer – Males : Bangalore

Age Adjusted Incidence Rates given in parentheses

1982-1983



2004-2005

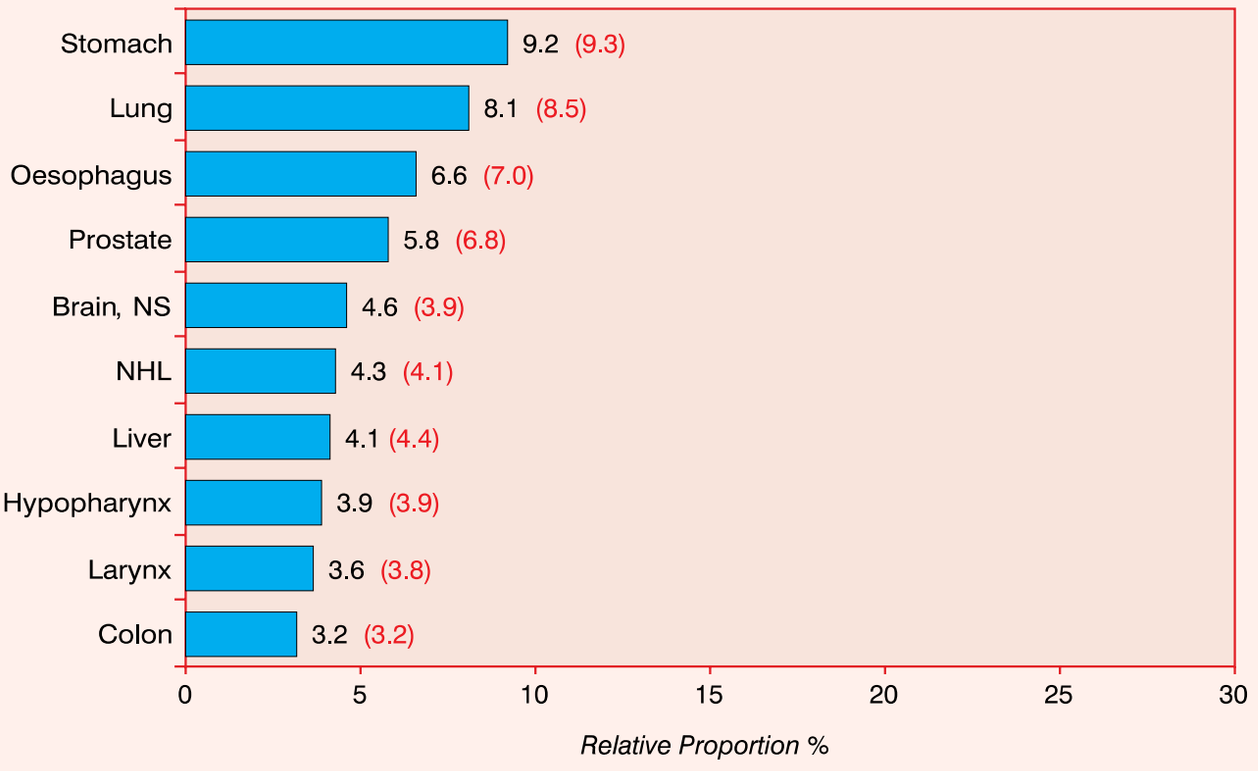
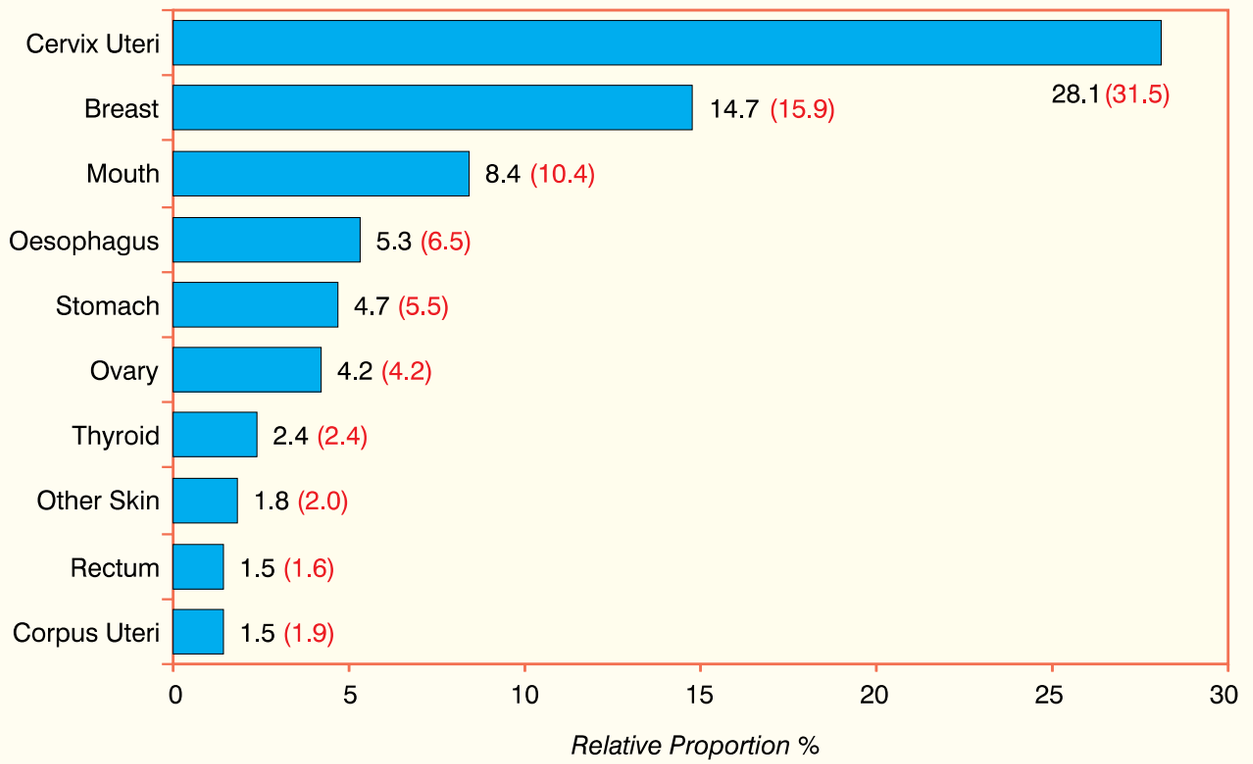


Fig. 3.1(b): Ten Leading Sites of Cancer – Females : Bangalore

Age Adjusted Incidence Rates given in parentheses

1982-1983



2004-2005

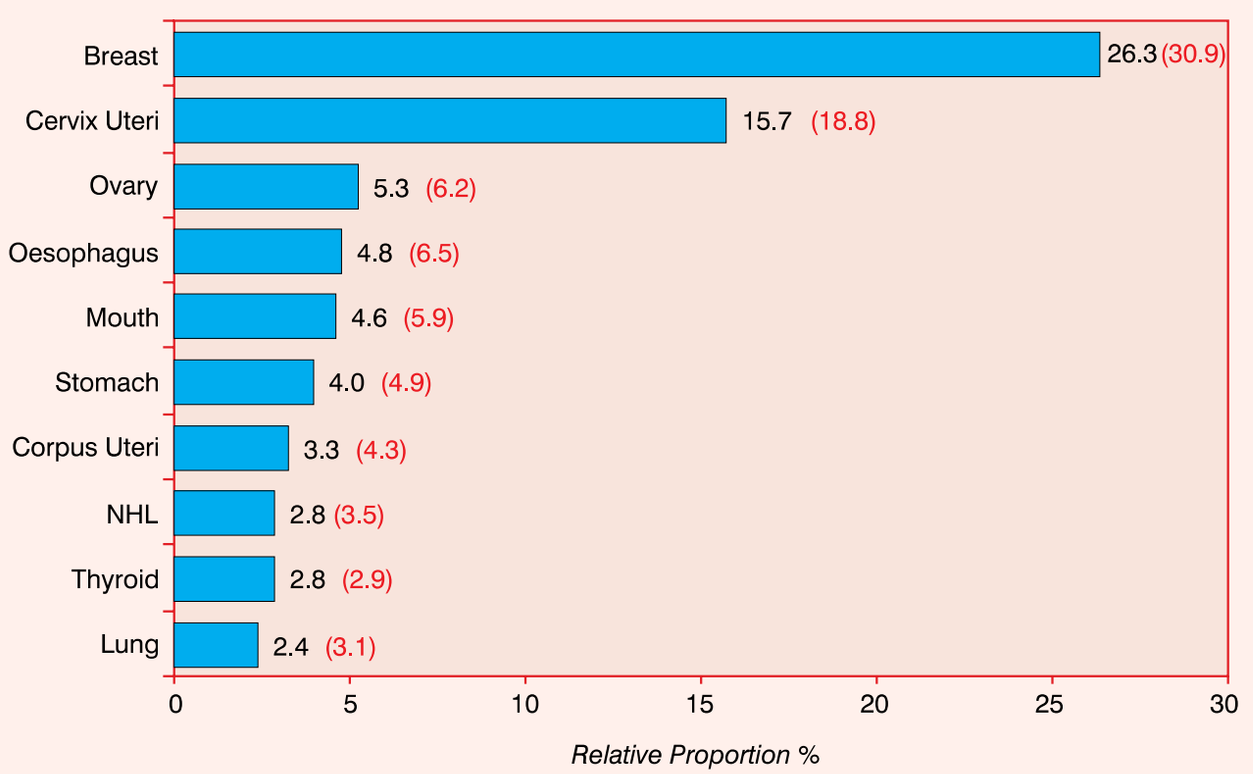
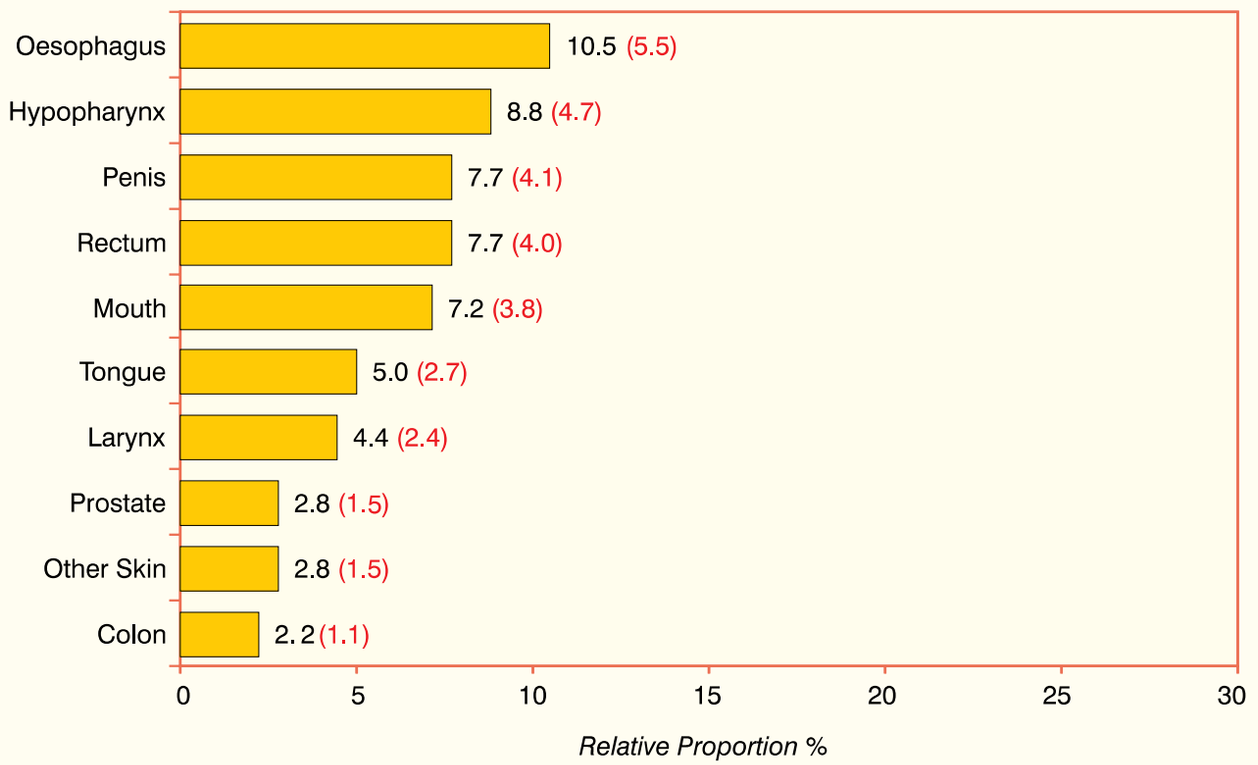


Fig. 3.2(a): Ten Leading Sites of Cancer – Males : Barshi

Age Adjusted Incidence Rates given in parentheses

1988-1989



2004-2005

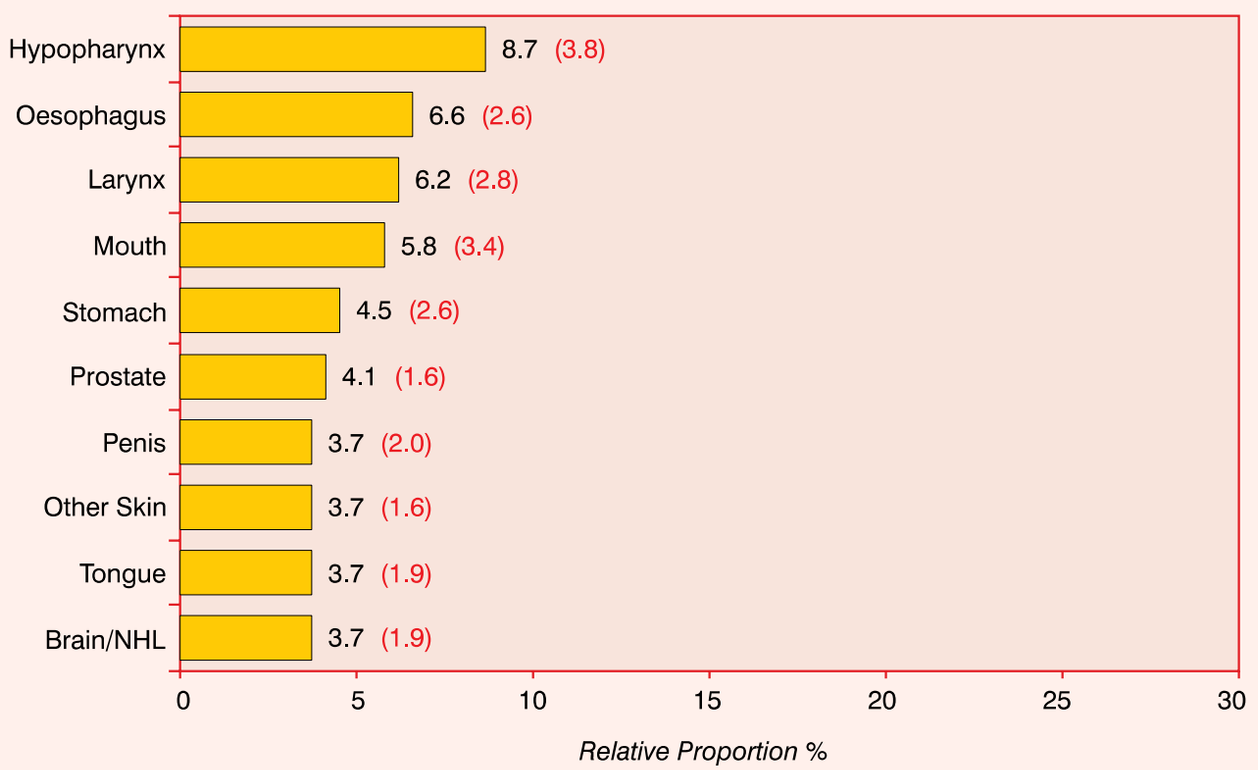
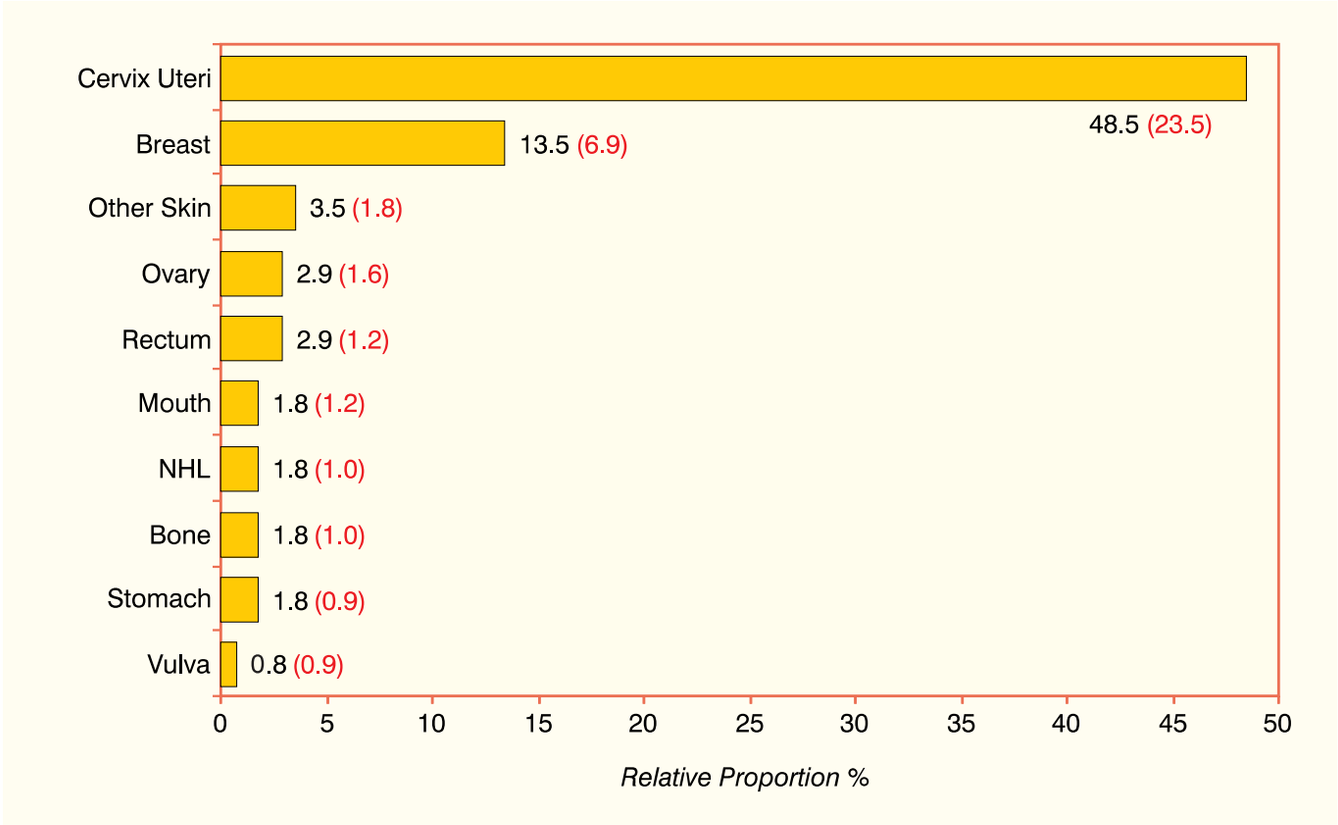


Fig. 3.2(b): Ten Leading Sites of Cancer – Females : Barshi

Age Adjusted Incidence Rates given in parentheses

1988-1989



2004-2005

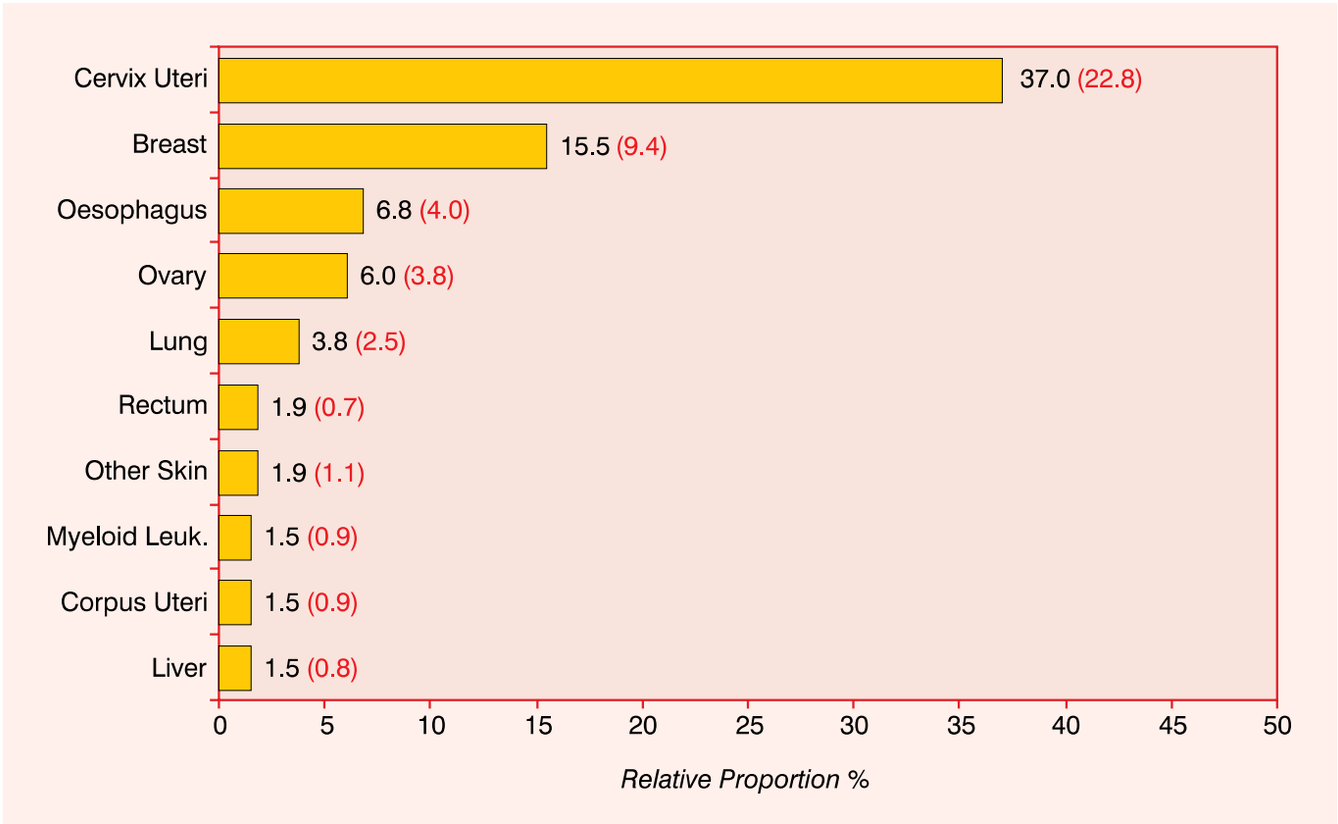
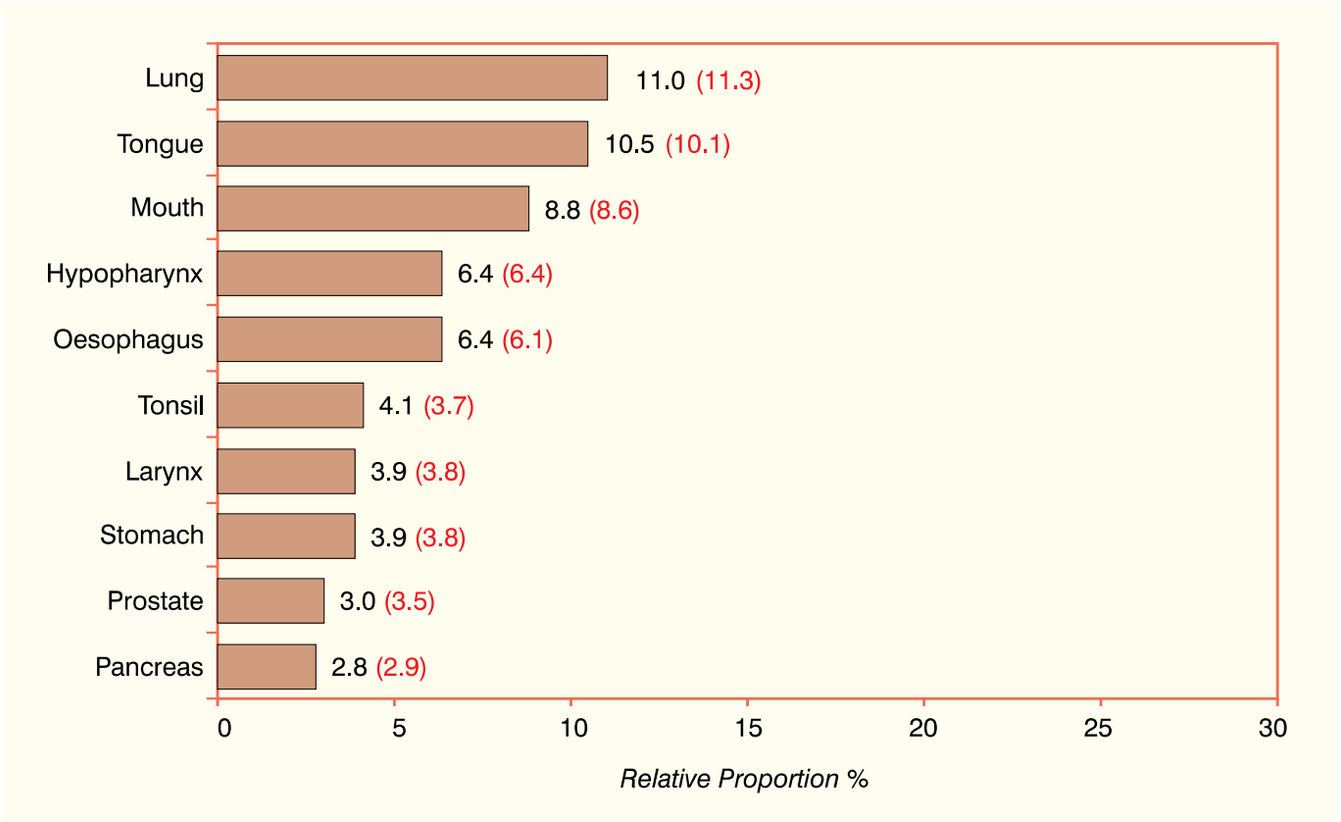


Fig. 3.3(a): Ten Leading Sites of Cancer – Males : Bhopal

Age Adjusted Incidence Rates given in parentheses

1988-1989



2004-2005

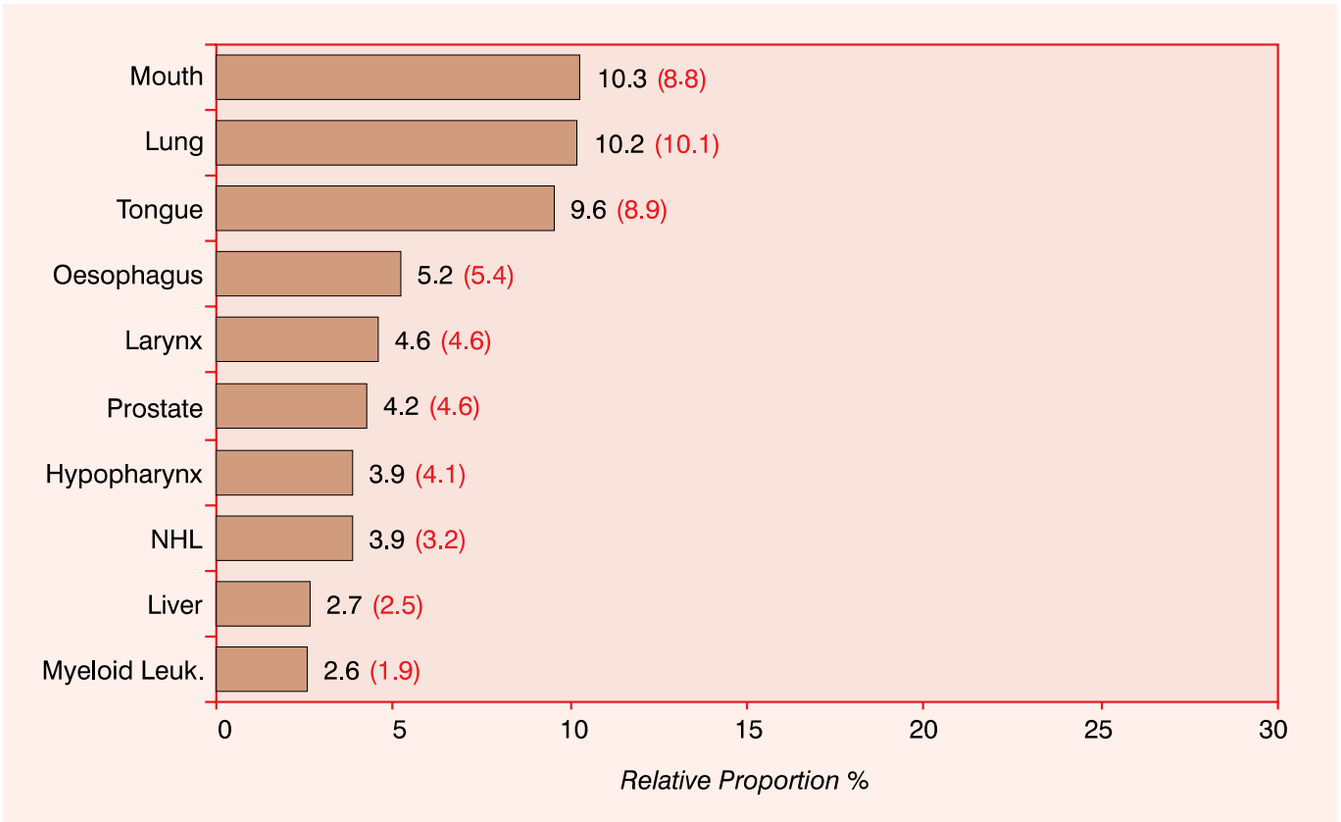
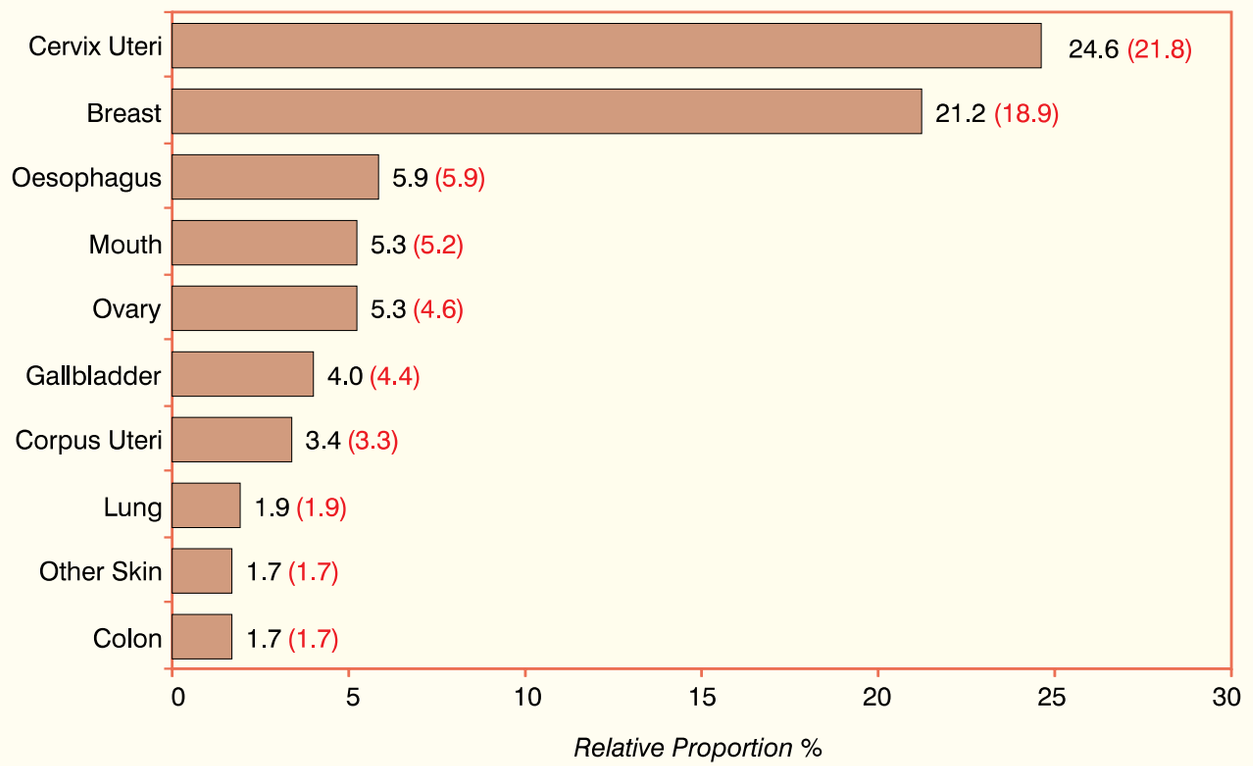


Fig. 3.3(b): Ten Leading Sites of Cancer – Females : Bhopal

Age Adjusted Incidence Rates given in parentheses

1988-1989



2004-2005

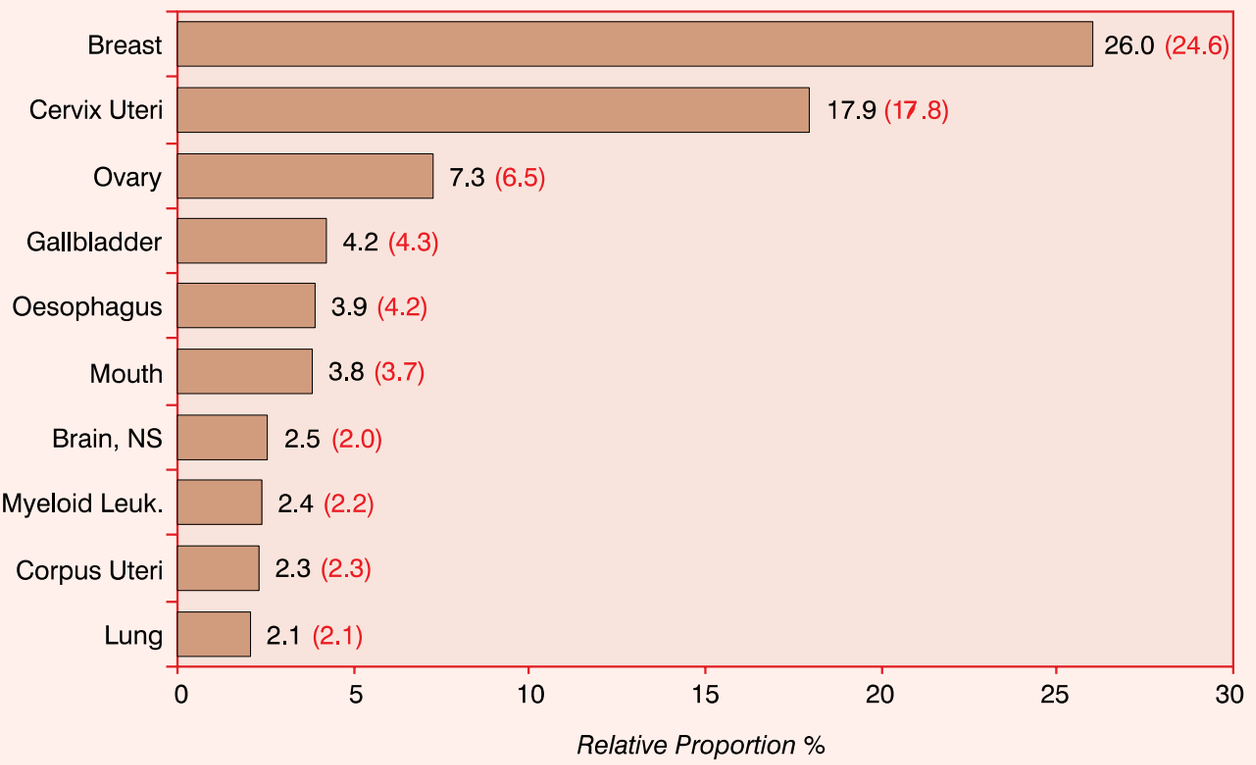
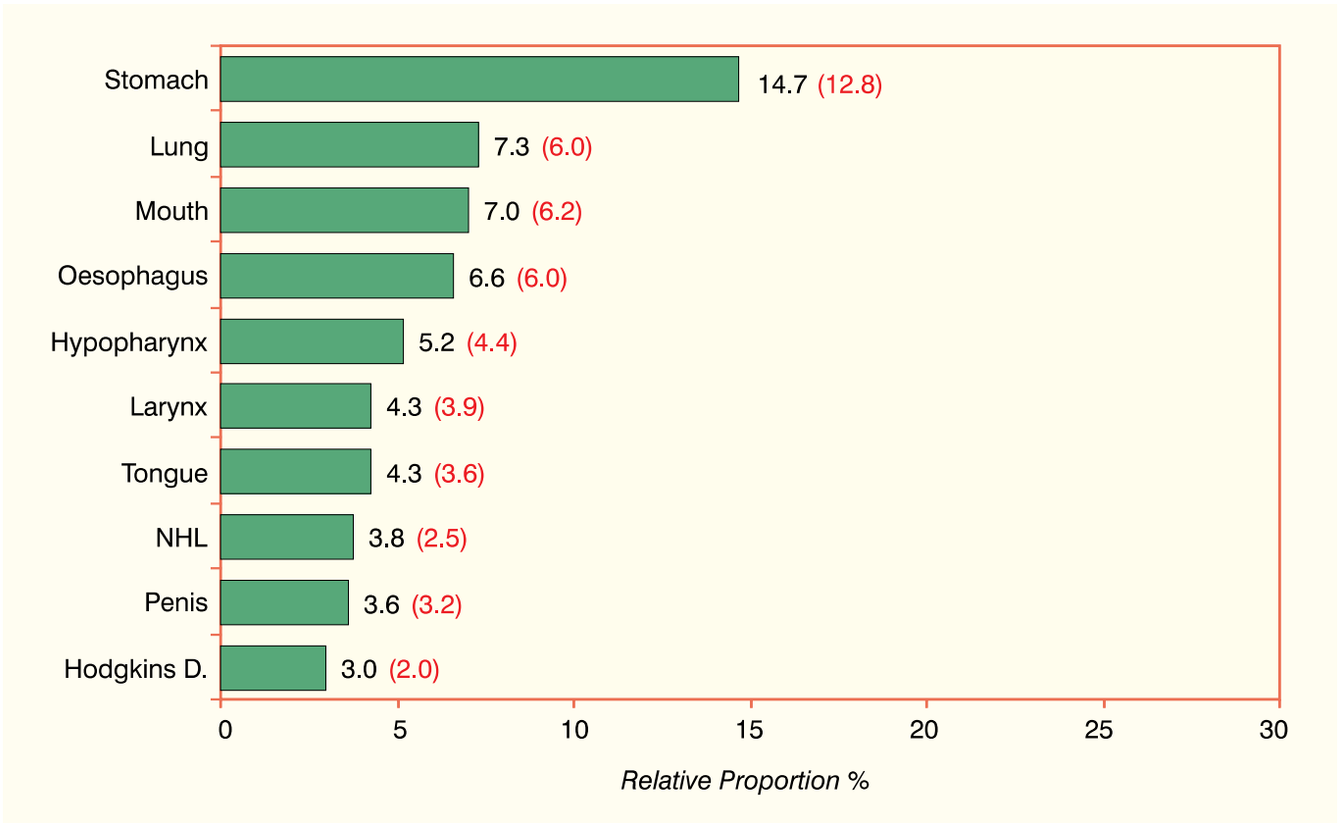


Fig. 3.4(a): Ten Leading Sites of Cancer – Males : Chennai

Age Adjusted Incidence Rates given in parentheses

1982-1983



2004-2005

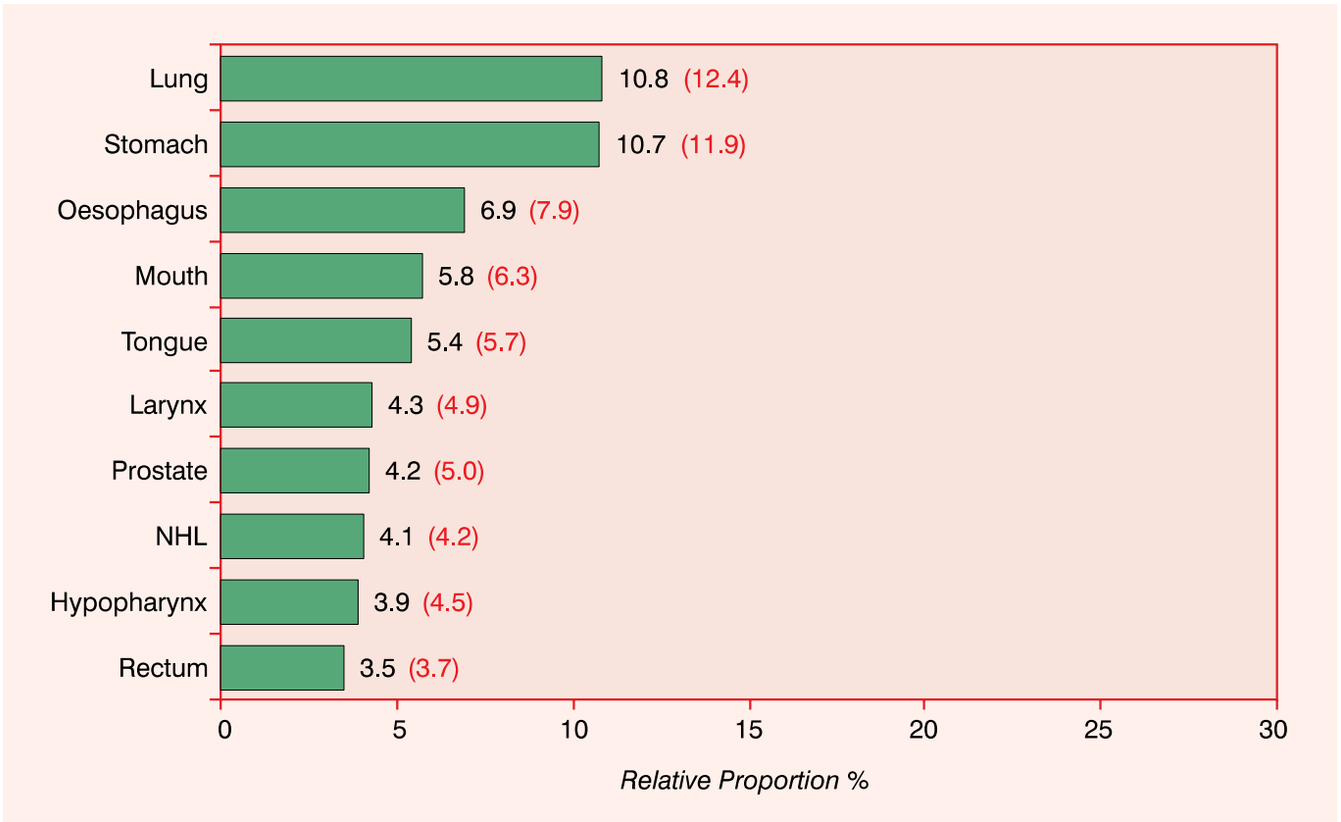
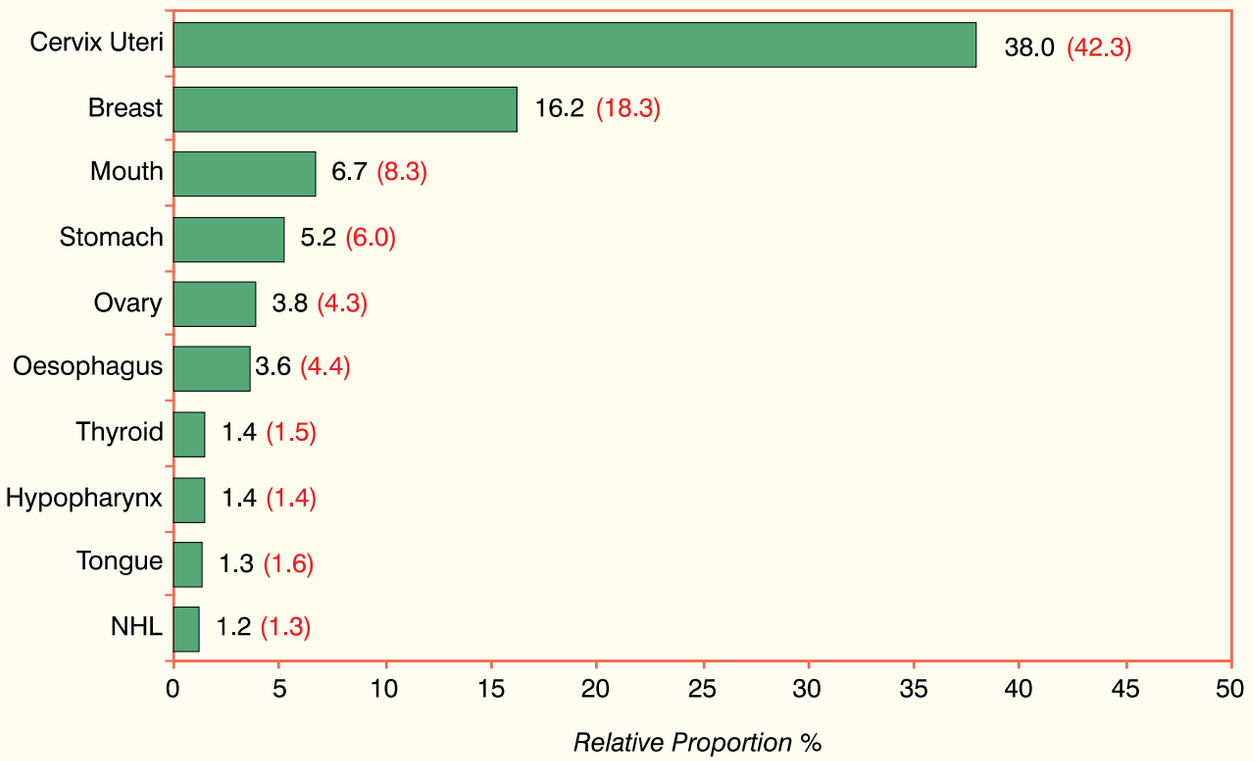


Fig. 3.4(b): Ten Leading Sites of Cancer – Females : Chennai

Age Adjusted Incidence Rates given in parentheses

1982-1983



2004-2005

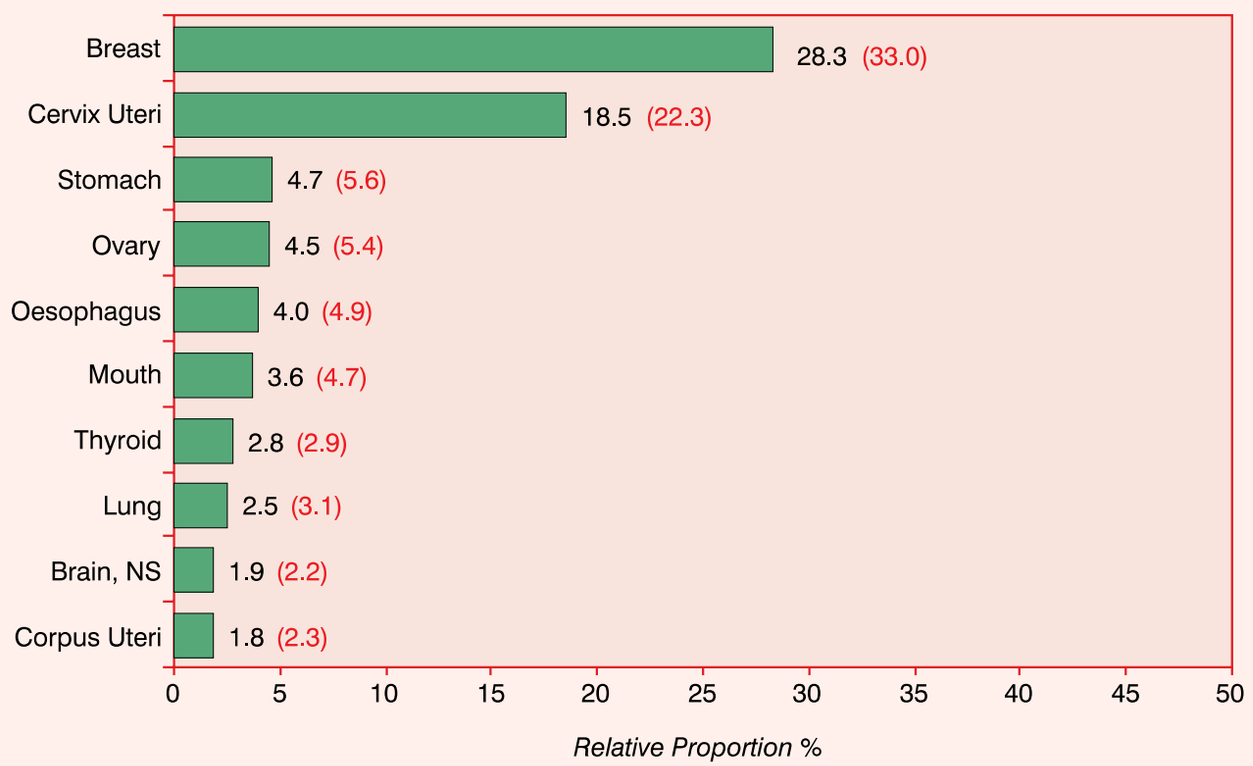
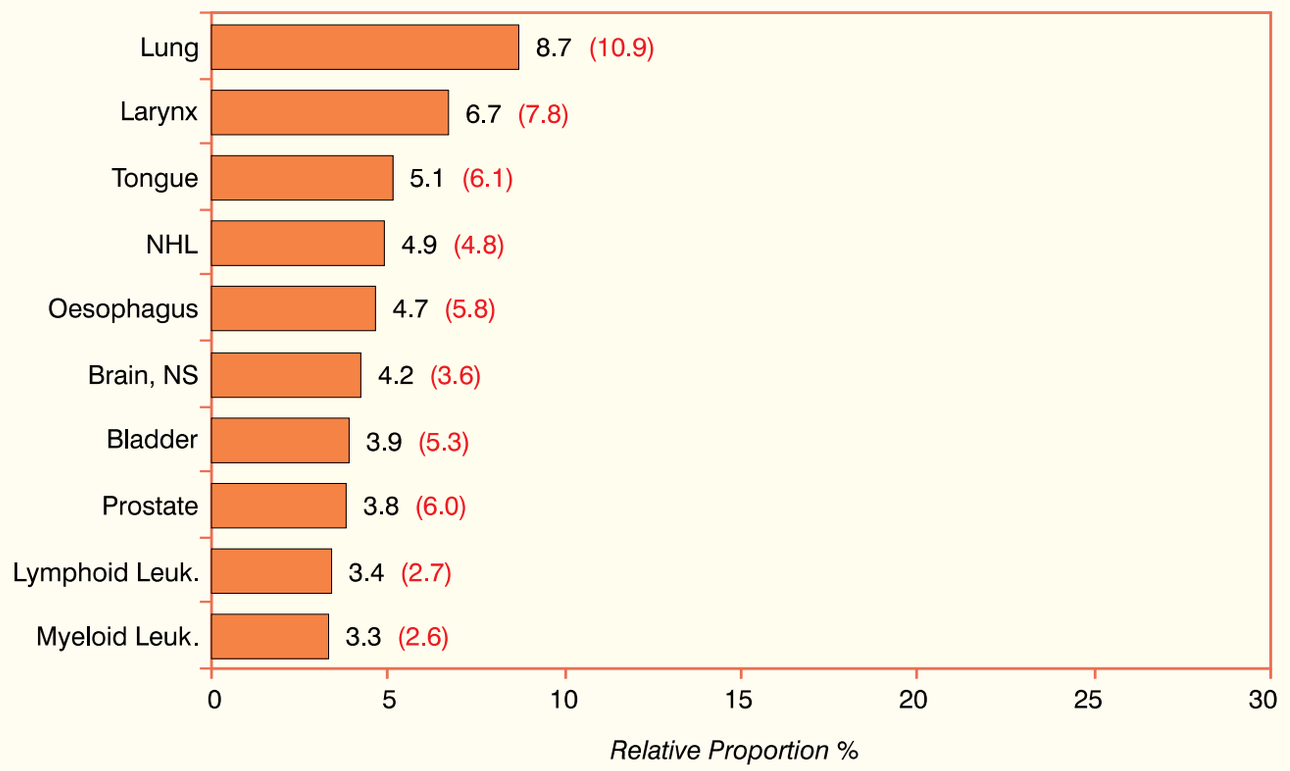


Fig. 3.5(a): Ten Leading Sites of Cancer – Males : Delhi

Age Adjusted Incidence Rates given in parentheses

1988-1989



2004-2005

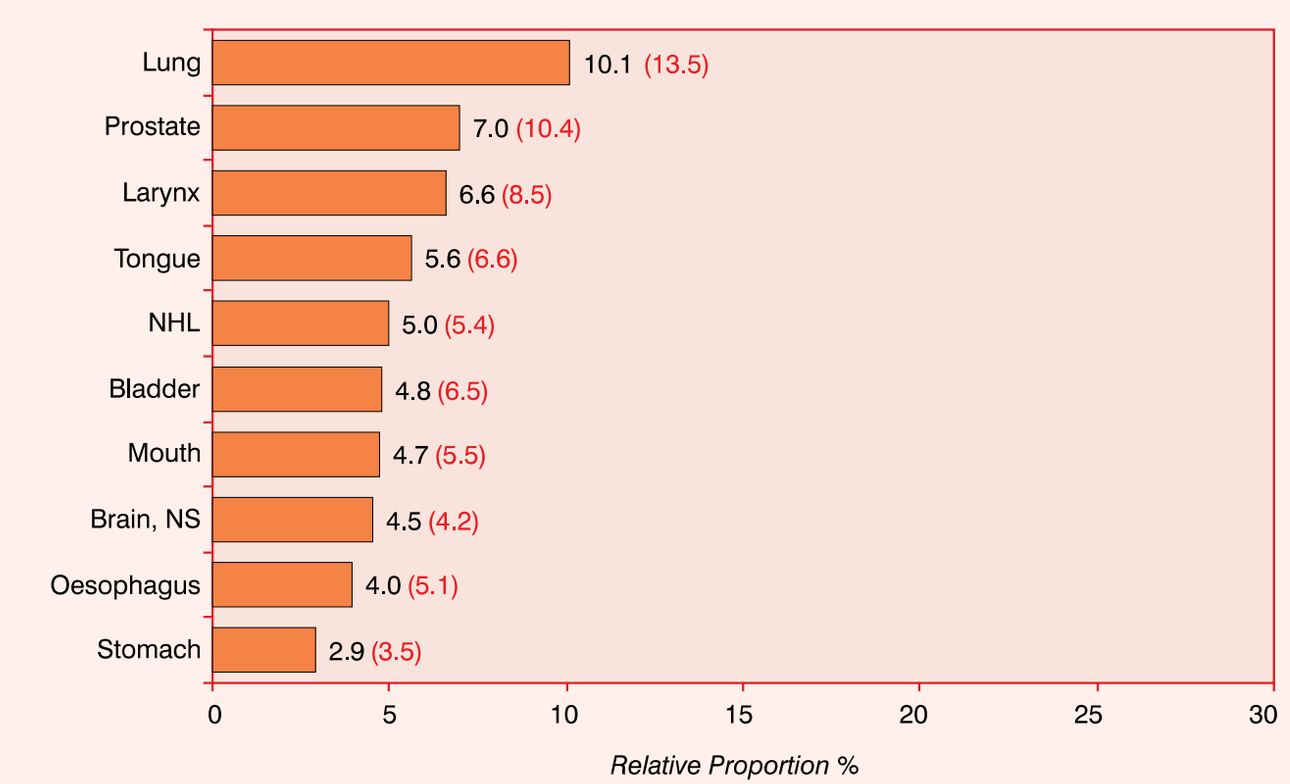
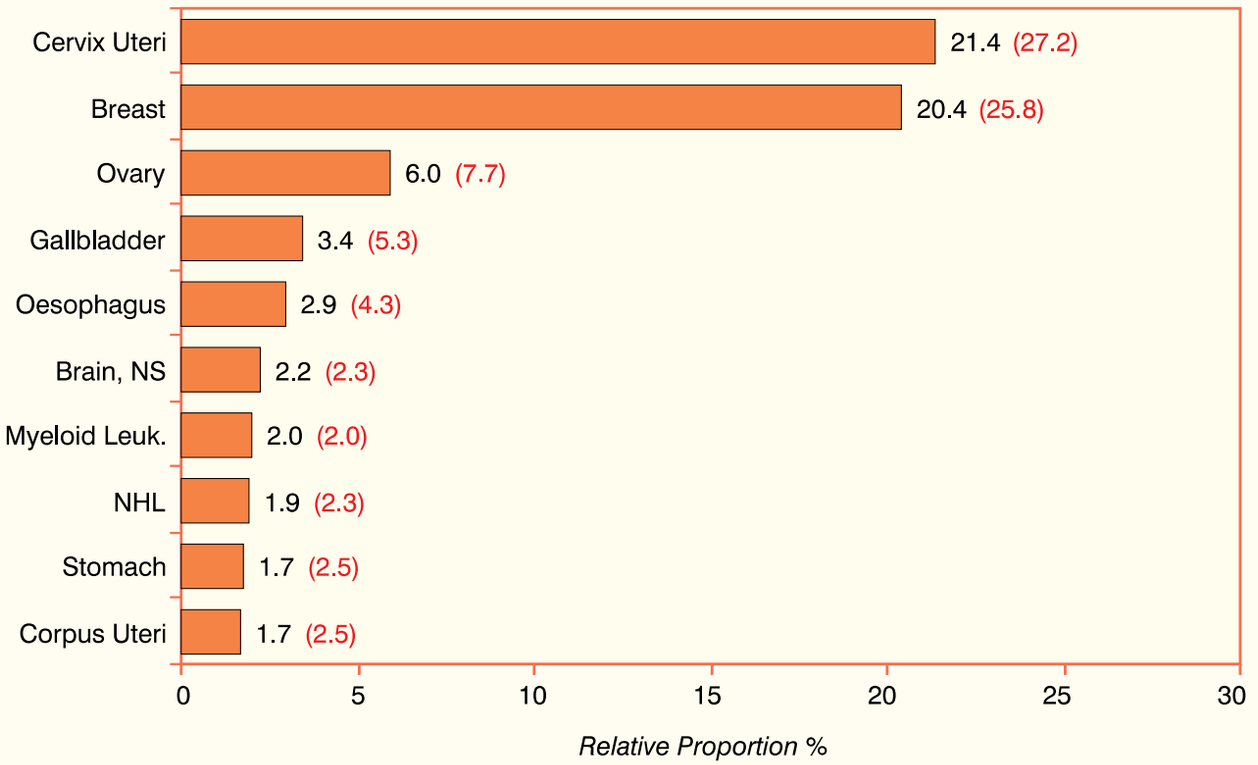


Fig. 3.5(b): Ten Leading Sites of Cancer – Females : Delhi

Age Adjusted Incidence Rates given in parentheses

1988-1989



2004-2005

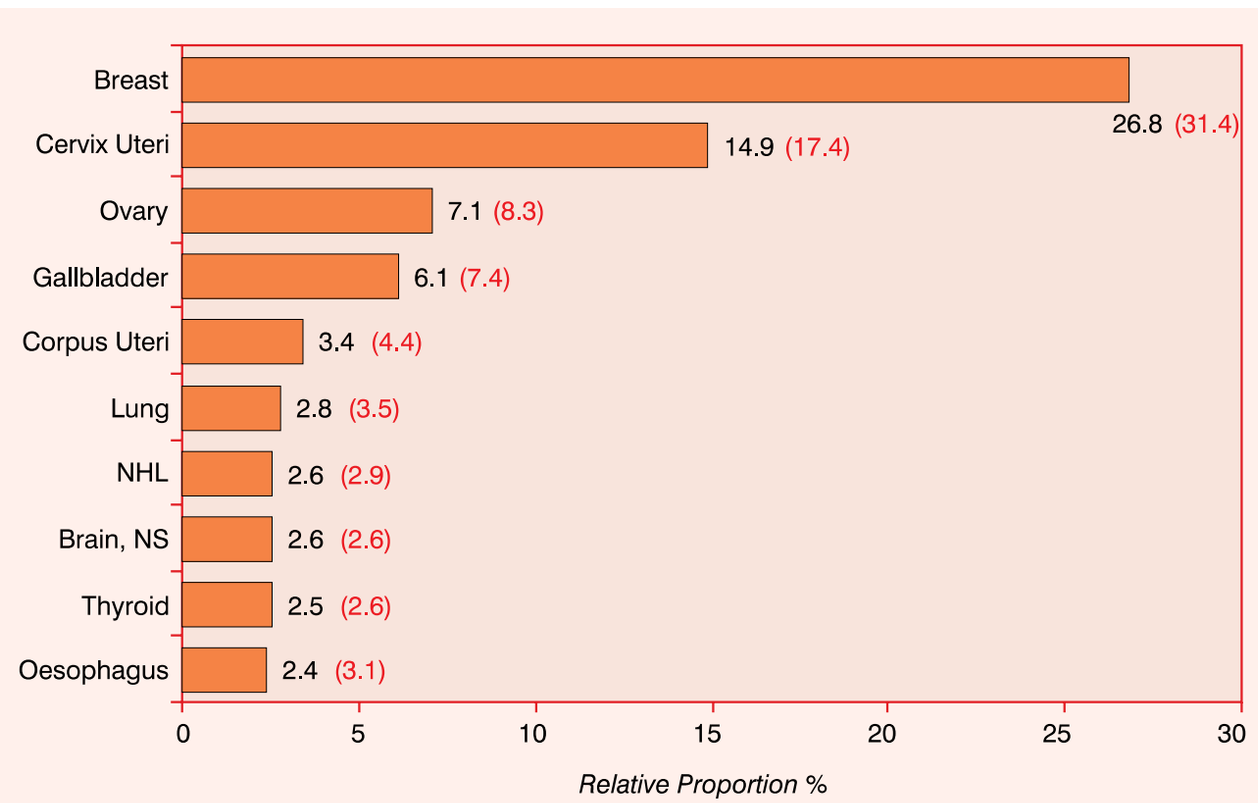
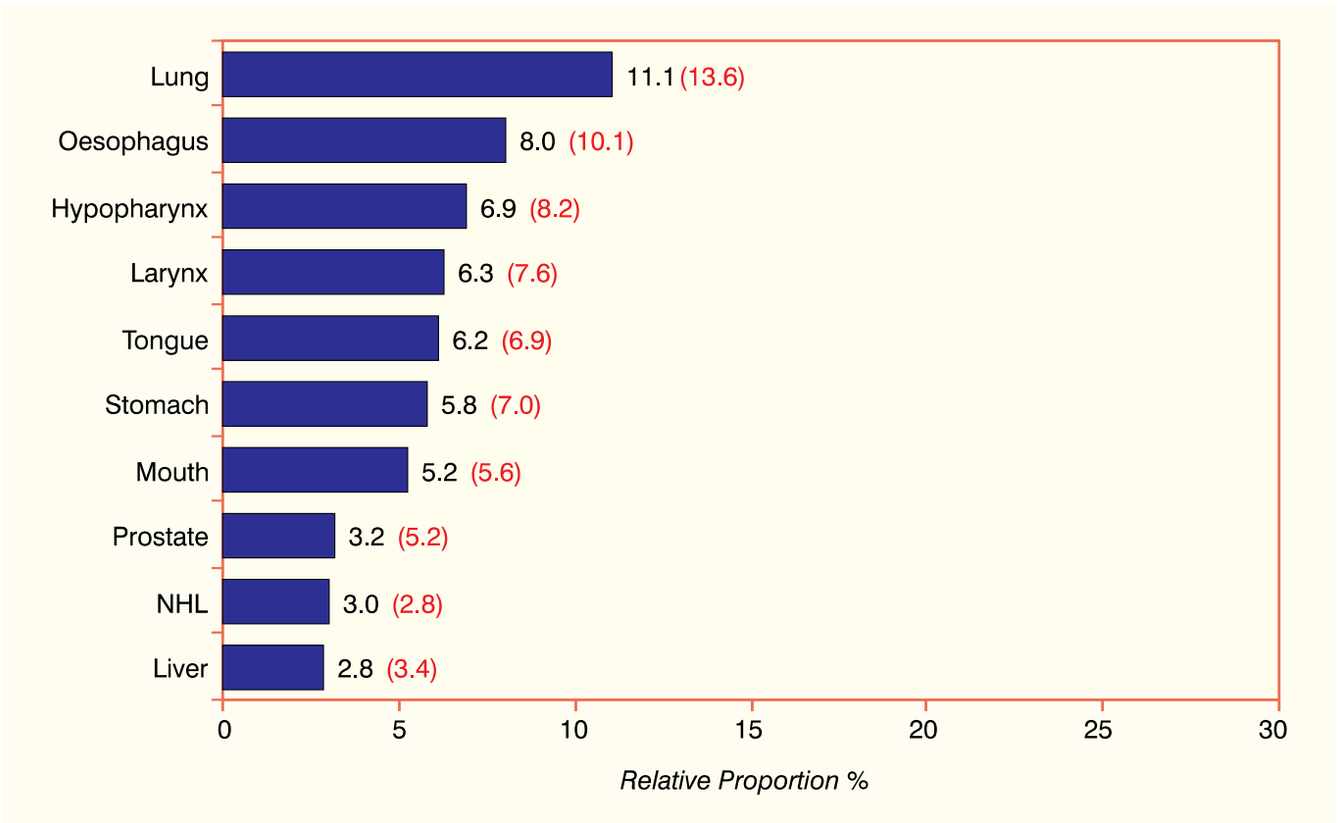


Fig. 3.6(a): Ten Leading Sites of Cancer – Males : Mumbai

Age Adjusted Incidence Rates given in parentheses

1982-1983



2004-2005

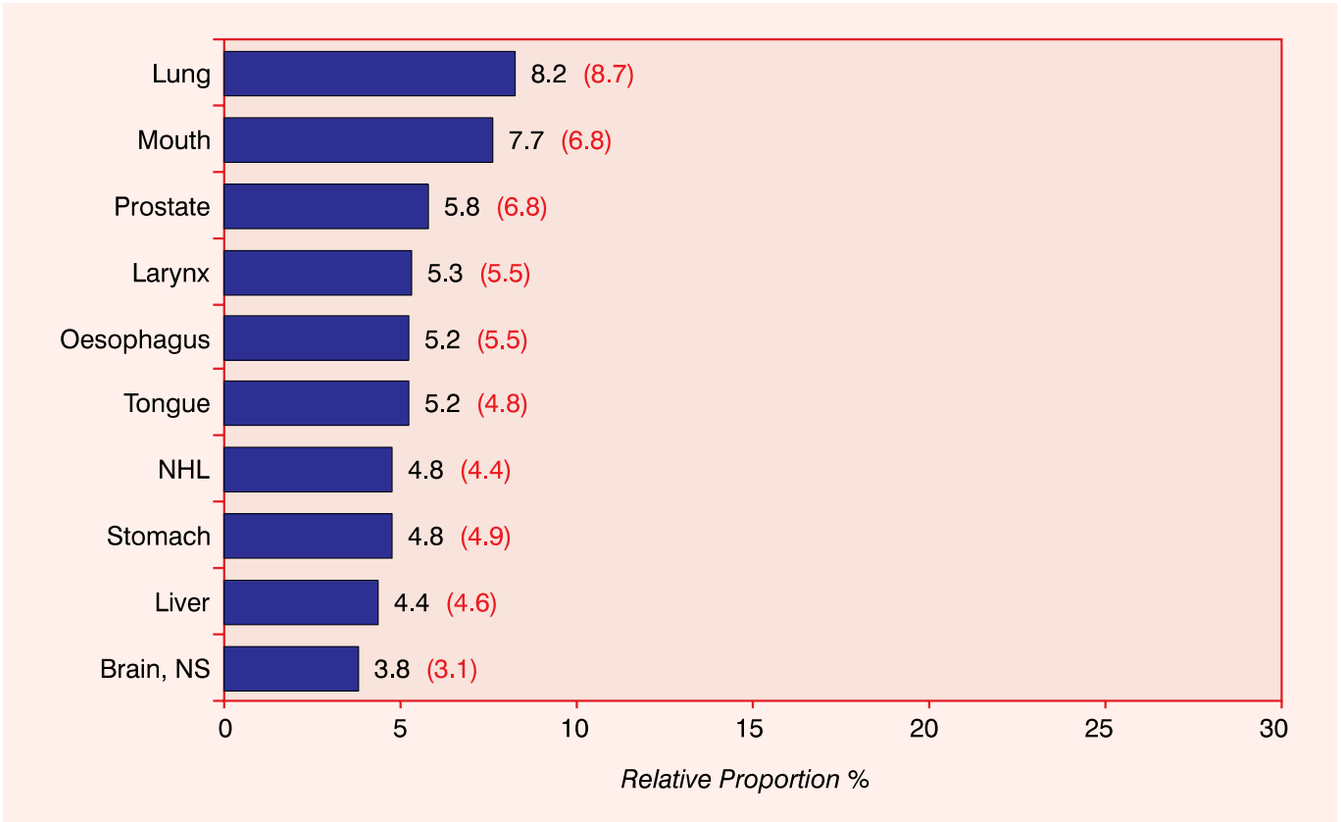
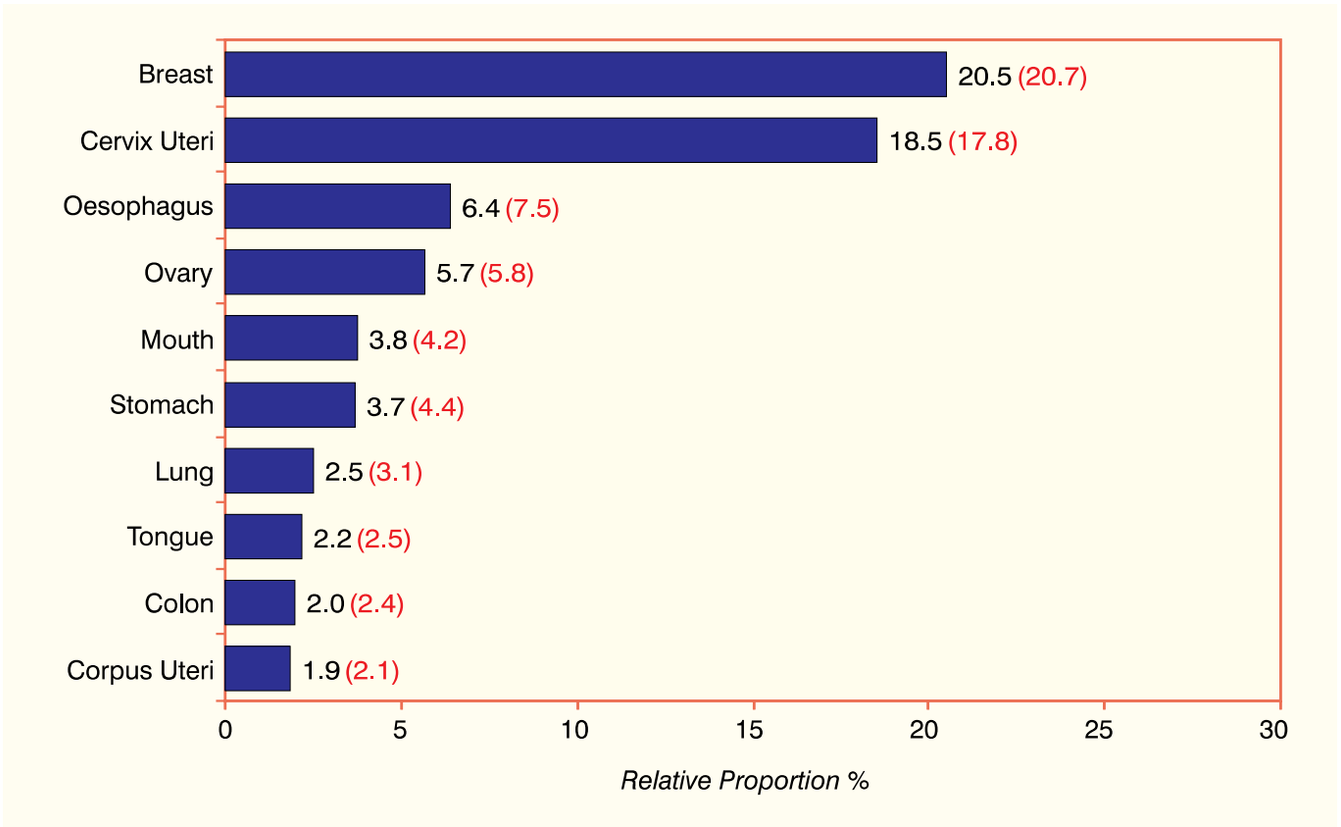


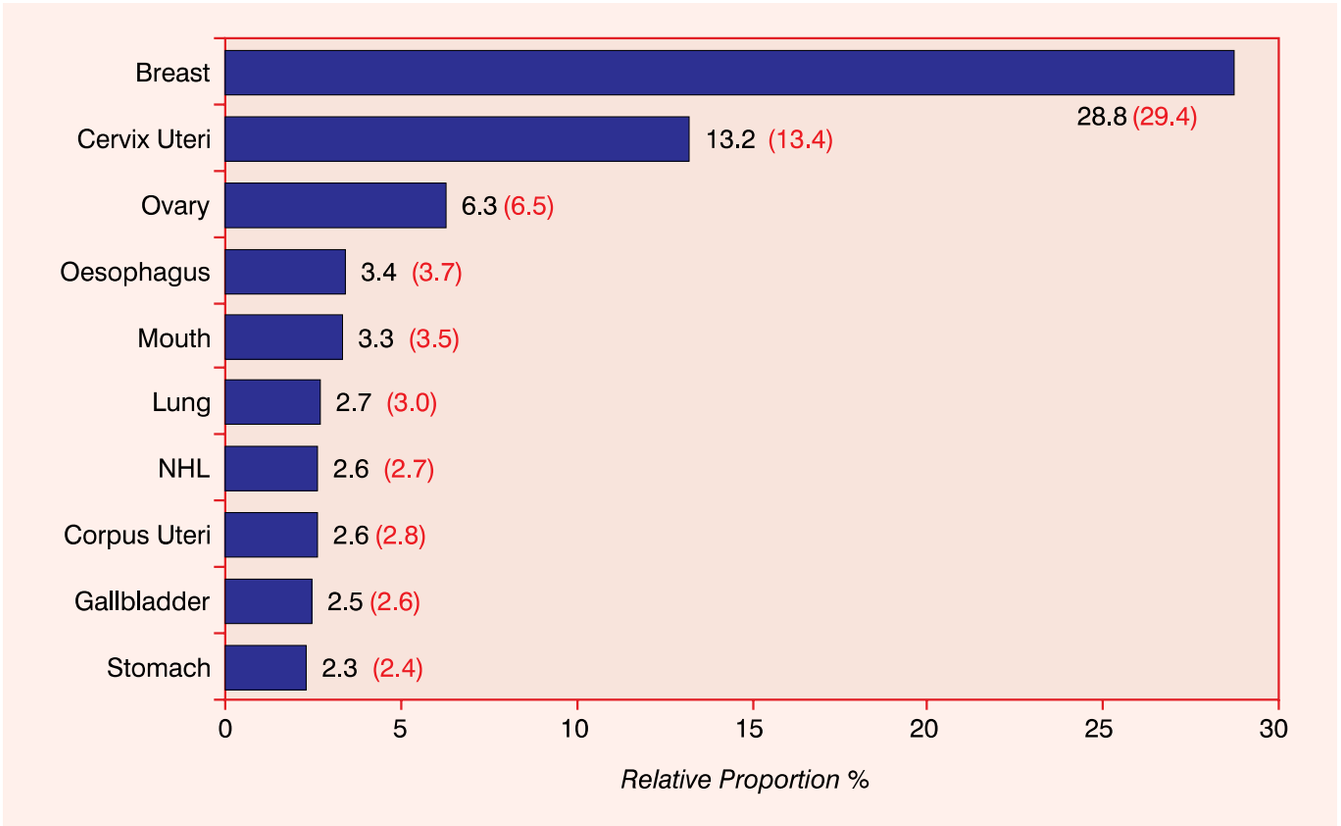
Fig. 3.6(b): Ten Leading Sites of Cancer – Females : Mumbai

Age Adjusted Incidence Rates given in parentheses

1982-1983



2004-2005



Chapter 4

TRENDS OVER TIME FOR ALL SITES AND ON SELECTED LEADING SITES OF CANCER

As mentioned in Chapter 2 the following sites have been included / excluded for the Barshi and Bhopal registries. In principle, anatomical sites with small numbers (less than ten cases per year) have been excluded.

For Barshi registry, only the following have been included:

(a) All anatomical sites (combined) in both males and females.
(b) Cancer of the breast and cervix in females.

All other sites have been excluded due to small numbers.

The following anatomical sites were excluded for Bhopal PBCR on account of small numbers. For males, the sites excluded were stomach, colon, rectum, liver, lymphoid and myeloid leukaemia. For females, the sites excluded were lung, corpus uteri, brain, NHL, thyroid gland and myeloid leukaemia. Certain other sites in Bhopal PBCR such as mouth in females, oesophagus in both males & females and Brain-NS in males have numbers in the teens and included. This needs to be kept in mind while interpreting the results.

Besides, in general, the ten leading sites of cancer across all registries have been chosen to depict trends over time.

Format of presentation for all sites and each of the selected anatomical sites :

The line graphs based on three year moving averages with the table below is shown on the left hand page. The facing page on the right shows Joinpoint Regression Model Trend lines with the corresponding table.

The table below the graph on three year Moving Average shows (i) the actual AAR values for each PBCR according to calendar year (ii) value of b (slope) and (iii) p-value with the values based on linear regression. In the facing page, the table below the Joinpoint Regression line gives the expected AAR values with respective Annual Percent Change (APC).

All Sites (Figure 4.1, 4.2 and Table 4.1, 4.2) :

Males: Both linear regression and joinpoint regression model did not show statistically significant increase or decrease in AAR over time in Bangalore, Barshi, Bhopal and Delhi PBCRs. Chennai PBCR showed a

significant rise in AAR over time. For the period 1982-1988, the APC was higher (4.5%) while from 1989–2005 this was 0.28%. Mumbai PBCR showed relative stable rates till 1990 with a decline thereafter.

Females: The PBCRs at Bangalore, Barshi, Bhopal and Chennai did not show a statistically significant change from 1982–2005. A statistically significant decline in AAR was observed for Delhi and Mumbai PBCR. For Mumbai PBCR, there was initial period of rise in AARs from 1982–1992, followed by a decline from 1993–2005.

Tongue (Figure 4.3 and Table 4.3) :

Males: There was no change in incidence rates trend over time for PBCRs of Bangalore, Bhopal and Delhi. Chennai showed an increasing trend whereas Mumbai showed a decline. The APC for Chennai was 1.3 and for Mumbai -2.0.

Mouth (Figure 4.4, 4.5 and Table 4.4, 4.5) :

Males: A rising trend was observed in both Delhi and Mumbai PBCR. The overall APC was 2.0 and 0.9 for Delhi and Mumbai respectively. The APC for Mumbai was higher (APC: 3.98) during later years (1998-2005).

Females: The registries at Bangalore, Delhi, Chennai and Mumbai showed a decline. The APC varied from -0.8 in Mumbai to -3.2 at Bangalore.

Hypopharynx (Figure 4.6 and Table 4.6) :

Males: The three PBCRs at Bangalore, Bhopal and Mumbai showed a decline in the AARs. The APC varied from -1.4 in Bangalore to -4.2 in Mumbai.

Oesophagus (Figure 4.7, 4.8 and Table 4.7, 4.8) :

Males: Only Delhi and Mumbai PBCRs showed a change in the AAR with a decline. The APC was -1.3 in Delhi and -3.1 in Mumbai.

Females: Bangalore, Bhopal, Delhi and Mumbai showed a decline with the APC ranging from -1.2 in Bangalore to -3.5 in Mumbai.

Stomach (Figure 4.9 and Table 4.9) :

Males: The AARs were unchanged over time for Bangalore and Delhi, whereas a decline was seen in Chennai and Mumbai PBCRs. The APC was -0.9 for Chennai and -2.2 for Mumbai. The decrease in Chennai was greater (APC: -1.5) for the later years (1987-2005).

Colon (Figure 4.10 and Table 4.10) :

Males: The PBCRs at Bangalore, Chennai and Delhi showed a statistically significant increase in the incidence of colon cancer. The APC was 1.7 in Delhi and 2.2 at both Bangalore and Chennai PBCRs.

Rectum (Figure 4.11 and Table 4.11) :

Males: Both Bangalore and Chennai showed a statistically significant increase in incidence rate trends over time. The APC was 1.6 for Bangalore and 2.5 for Chennai.

Liver (Figure 4.12 and Table 4.12) :

Males: The four PBCRs at Bangalore, Chennai, Delhi and Mumbai showed a statistically significant increase in the incidence of this cancer. The APC varied from 1.6 in Chennai to 2.0 in Bangalore. In Mumbai the change was higher (APC: 2.6) for later years (1997-2005).

Gallbladder (Figure 4.13 and Table 4.13) :

Females: The PBCRs at Bangalore, Bhopal, Chennai and Mumbai showed a statistically significant increase in the incidence of gallbladder cancer. The APC varied from 2.5 in Mumbai to 5.9 in Bangalore and Chennai. In Delhi PBCR a 15% increase was observed annually from 1988–1993, but thereafter a significant decline was observed. In Mumbai the change (APC: 9.1) was more during the earlier years (1982-1991).

Larynx (Figure 4.14 and Table 4.14) :

Males: Bhopal PBCR showed a significant increase whereas Mumbai PBCR showed a significant decrease in incidence rates over the years. The APC for Bhopal was 2.9 and -1.5 for Mumbai.

Lung (Figure 4.15, 4.16 and Table 4.15, 4.16) :

Males: Chennai and Delhi PBCRs showed a statistically significant increase in AARs of lung cancer with APC being 2.3 in Chennai and 1.0 in Delhi. In Chennai the change was higher (APC: 8.2) during the years 1982-1990.

Females: The three PBCRs at Bangalore, Chennai and Delhi showed an increase in the incidence of lung cancer over time with the APC varying from 2.0 in Delhi to 4.6 in Chennai.

Breast – Females (Figure 4.17 and Table 4.17) :

All the urban registries at Bangalore, Bhopal, Chennai, Delhi and Mumbai showed statistically significant increase in the incidence of breast cancer. The APC varied from 1.0 in Delhi to 2.7 in Bangalore. In Chennai the increase was more (APC: 4.0) during the later years (1995-2005) while in Mumbai the increase was more (APC: 3.1) during earlier years (1982-1991).

Cervix (Figure 4.18 and Table 4.18) :

All the six PBCRs have recorded a statistically significant decline in the incidence rates of cancer cervix. This includes the rural registry at Barshi. The APC varied from -1.4 in Bhopal to -3.4 in Delhi.

Corpus Uteri (Figure 4.19 and Table 4.19) :

The four registries at Bangalore, Chennai, Delhi and Mumbai showed a statistically significant increase in the incidence of cancer of corpus uteri. The APC varied from 1.7 in Mumbai to 5.8 in Bangalore.

Ovary – Females (Figure 4.20 and Table 4.20) :

Bangalore and Mumbai PBCRs showed an increase in the occurrence of incidence rates of this cancer. The APC was 0.8 in Mumbai and 1.7 in Bangalore. The increase in Mumbai was more (APC: 2.64) during earlier years.

Prostate (Figure 4.21 and Table 4.21) :

The four registries at Bangalore, Chennai, Delhi and Mumbai showed a statistically significant increase in the incidence of prostate cancer with the APC varying from 0.8 in Mumbai to 4.7 in Chennai.

Brain (Figure 4.22, 4.23 and Table 4.22, 4.23) :

Males: The PBCRs at Bangalore, Chennai and Mumbai showed an increase in the AARs. The APC was 2.7 in Mumbai PBCR, 3.0 in Chennai PBCR and 3.2 in Bangalore PBCR.

Females: As in males, Bangalore, Chennai and Mumbai showed a statistically significant increase in the occurrence of this cancer. The APC was 2.9 in Mumbai and 3.4 in Bangalore and 4.6 in Chennai.

Thyroid Gland (Figure 4.24 and Table 4.24) :

Females: Chennai and Delhi PBCR recorded an increase with the APC being 2.2 in Delhi and 2.6 in Chennai. The increase in Chennai was more (APC: 8.23) during the years 1996-2005.

NHL (Figure 4.25, 4.26 and Table 4.25, 4.26) :

Males: All the five urban PBCRs showed a statistically significant increase in the incidence of NHL. The APC varied from 1.0 in Delhi to 7.9 in Bhopal.

Females: Bangalore, Chennai, Delhi and Mumbai PBCRs showed as in males, a statistically significant increase in the incidence of this cancer. The APC varied from 1.2 in Delhi to 3.6 in Bangalore. The increase in both Chennai (APC: 5.1) and Mumbai (APC: 4.1) was more during the early years (1982-97).

Lymphoid Leukaemia (Figure 4.27 and Table 4.27) :

Males: Bangalore and Chennai PBCRs recorded an increase in the incidence of this cancer with the APC being 2.6 in Chennai and 2.7 in Bangalore.

Myeloid Leukaemia (Figure 4.28, 4.29 and Table 4.28, 4.29) :

Males: PBCRs at Bangalore, Chennai and Mumbai showed an increase in AARs with the APC being 0.8 in Mumbai to 2.2 in Bangalore and 2.5 in Chennai.

Females: As in males, both Bangalore and Chennai showed an increase in incidence rates with the APC being 1.9 in Bangalore and 3.4 in Chennai.

Lung cancer in Chennai women increased annually at the rate of 4.6%.

Both Chennai and Bangalore recorded an APC of 5.8% increase annually in the incidence of gallbladder cancer.

Cancer of the breast increased at the rate of 4% annually in Chennai females from 1995 to 2005. Likewise Chennai females also recorded an annual percentage increase of 8.2 for Thyroid cancers during 1995-2005.

Fig. 4.1(a): ALL SITES (ICD-10 : C00-C96) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

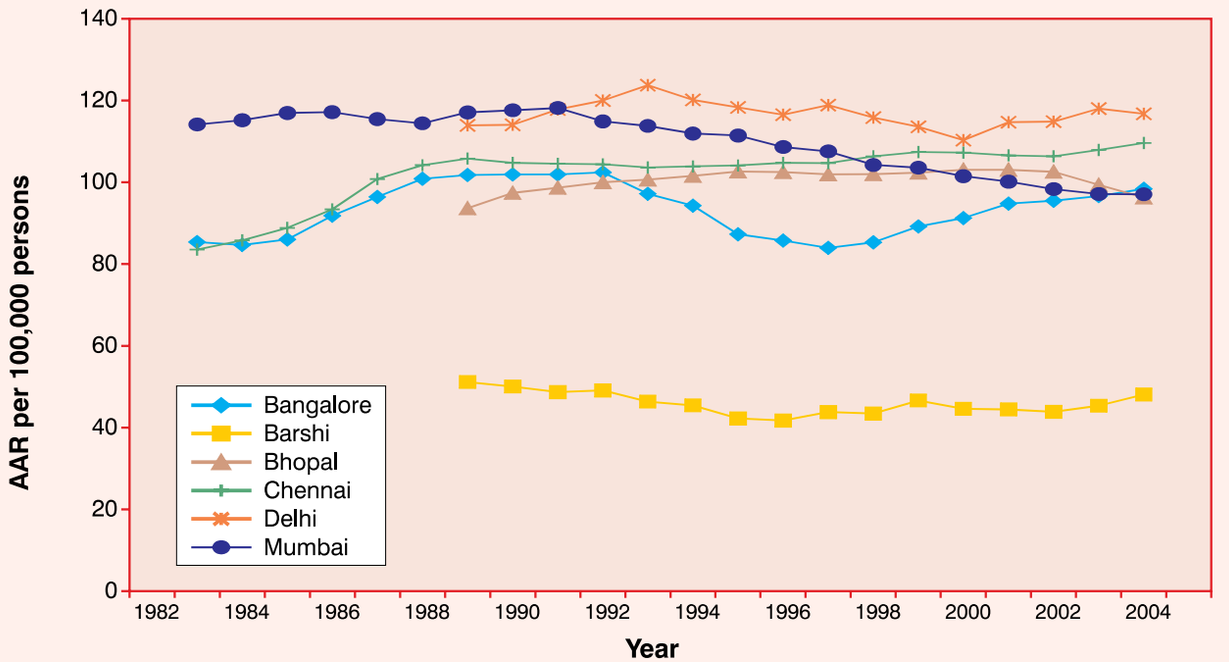


Table 4.1(a): Year wise AARs

Year	Bangalore	Barshi	Bhopal	Chennai	Delhi	Mumbai
1982	90.7			80.2		115.9
1983	83.5			85.9		110.9
1984	81.8			84.6		115.7
1985	88.7			87.0		119.0
1986	87.4			94.9		116.3
1987	99.3			98.3		116.2
1988	102.5	51.2	88.9	109.1	111.3	113.9
1989	100.8	51.4	95.9	105.2	112.5	113.1
1990	101.9	50.9	96.1	103.2	117.9	124.3
1991	103.0	47.8	100.3	105.9	111.8	115.2
1992	100.8	47.4	99.7	104.6	123.6	115.0
1993	103.4	52.1	100.0	102.6	124.5	114.5
1994	87.3	39.6	102.2	103.6	123.0	111.9
1995	92.2	44.7	102.4	105.5	112.9	109.4
1996	82.3	42.5	103.2	103.3	119.0	113.0
1997	82.7	38.2	101.8	105.4	117.8	103.6
1998	87.0	50.8	100.8	105.4	120.0	106.2
1999	86.1	41.4	103.4	108.3	109.8	103.0
2000	94.4	47.7	102.7	108.7	110.9	101.4
2001	93.3	44.7	103.0	104.8	110.3	100.1
2002	96.7	40.8	103.3	106.2	123.0	99.0
2003	96.5	46.0	101.4	108.2	111.3	95.8
2004	96.7	49.3	93.3	109.4	119.8	96.6
2005	102.0	49.1	94.1	111.3	119.2	98.6
Slope(b)	**0.169**	**-0.247**	**0.208**	**0.986**	**0.019**	**-0.961**
p-value	0.451	0.228	0.287	**0.001**	0.938	**0.001**

Fig. 4.1(b): ALL SITES (ICD-10 : C00-C96) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

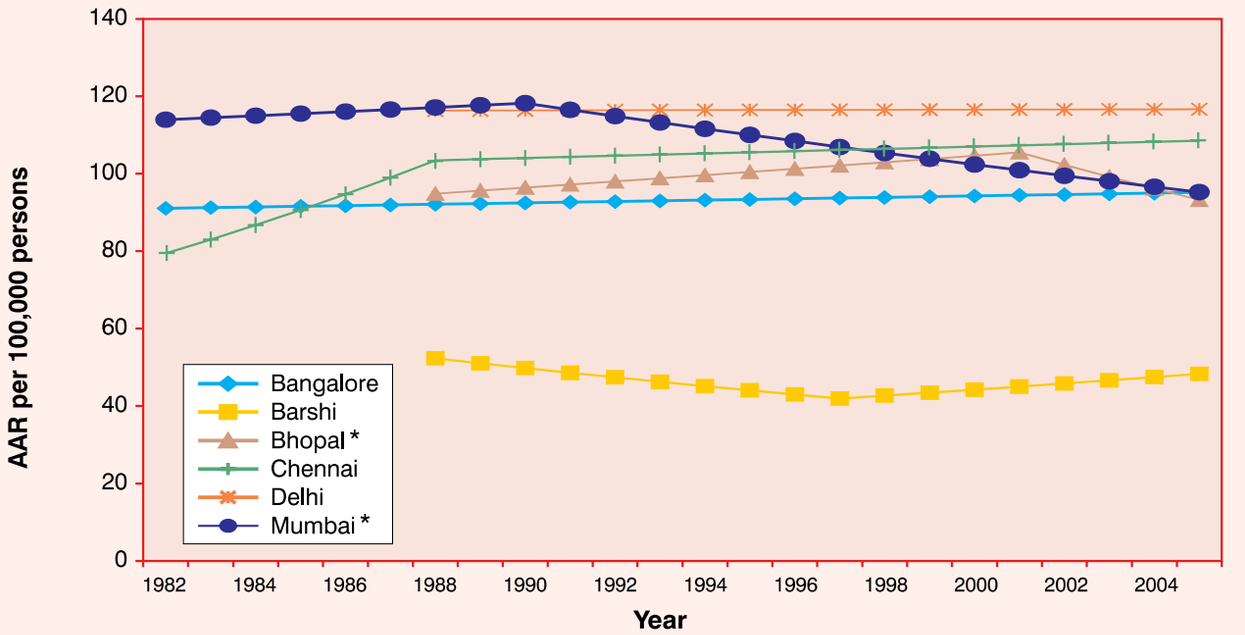


Table 4.1(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Barshi	Bhopal	Chennai	Delhi	Mumbai
	JP0*	**JP1***	**JP1***	**JP1***	**JP0***	**JP1***
1982	91.1			79.4		113.9
1983	91.2			83.0		114.5
1984	91.4			86.7		115.0
1985	91.6			90.6		115.5
1986	91.8			94.7		116.1
1987	91.9			99.0		116.6
1988	92.1	52.3	94.9	**103.4**	116.3	117.1
1989	92.3	51.1	95.6	103.7	116.3	117.7
1990	92.5	49.8	96.4	104.0	116.4	**118.2**
1991	92.7	48.6	97.2	104.3	116.4	116.5
1992	92.8	47.4	98.0	104.6	116.4	114.9
1993	93.0	46.3	98.8	104.9	116.4	113.2
1994	93.2	45.2	99.6	105.2	116.4	111.6
1995	93.4	44.1	100.4	105.5	116.5	110.0
1996	93.5	43.0	101.3	105.8	116.5	108.4
1997	93.7	**42.0**	102.1	106.1	116.5	106.9
1998	93.9	42.7	102.9	106.4	116.5	105.4
1999	94.1	43.5	103.8	106.7	116.5	103.8
2000	94.3	44.3	104.6	107.0	116.6	102.4
2001	94.4	45.0	**105.5**	107.3	116.6	100.9
2002	94.6	45.8	102.3	107.6	116.6	99.5
2003	94.8	46.7	99.2	107.9	116.6	98.0
2004	95.0	47.5	96.2	108.2	116.6	96.6
2005	95.2	48.3	93.3	108.5	116.7	95.3
APC0	0.19	-0.52	0.21	**1.03***	0.02	**-0.89***
APC1	–	**-2.42***	**0.82***	**4.50***	–	0.46
APC2	–	1.78	**-3.04***	**0.28***	–	**-1.43***

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.2(a): ALL SITES (ICD-10 : C00-C96) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

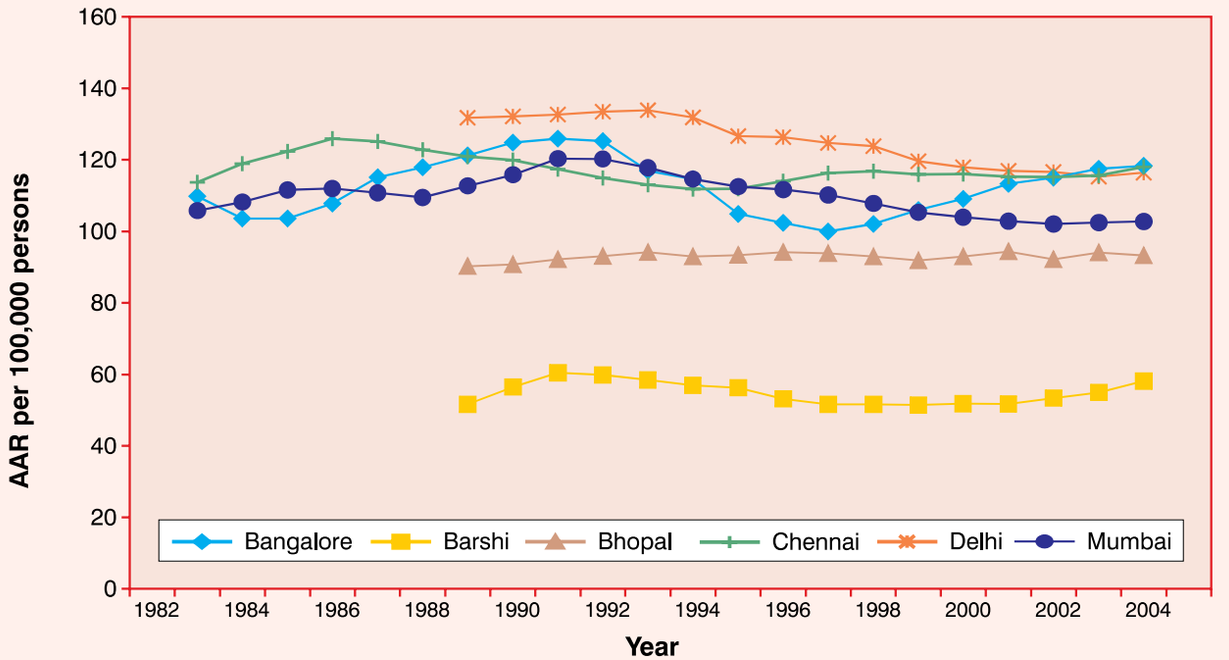


Table 4.2(a): Year wise AARs

Year	Bangalore	Barshi	Bhopal	Chennai	Delhi	Mumbai
1982	117.5			106.2		107.7
1983	105.8			118.6		101.8
1984	105.9			116.4		107.8
1985	98.9			121.9		115.0
1986	105.9			128.8		112.0
1987	118.4			127.1		109.0
1988	121.0	48.9	89.5	119.4	127.0	111.2
1989	114.2	49.7	90.1	121.8	133.1	108.4
1990	128.4	56.3	90.9	121.6	135.3	118.6
1991	131.9	63.3	91.3	116.4	128.0	120.6
1992	117.6	61.8	94.1	114.2	134.5	121.8
1993	126.3	54.4	93.6	114.0	137.7	118.1
1994	106.8	59.2	94.6	110.9	129.2	113.5
1995	110.8	57.4	90.6	110.6	128.7	112.0
1996	97.2	52.1	94.7	114.1	122.0	111.9
1997	99.3	50.0	97.2	117.3	128.4	111.2
1998	103.4	52.9	89.6	117.6	123.9	107.3
1999	103.5	51.9	92.0	115.5	119.1	104.7
2000	110.9	49.7	93.8	114.7	116.0	103.8
2001	112.9	54.0	93.1	117.9	118.7	103.3
2002	116.1	51.7	96.3	113.3	116.1	101.6
2003	116.1	54.5	87.2	114.5	114.9	101.2
2004	120.2	58.7	98.8	119.0	114.8	104.6
2005	118.6	61.2	93.7	120.4	119.4	102.4
Slope(b)	**0.049**	**0.037**	**0.192**	**-0.134**	**-1.190**	**-0.358**
p-value	0.865	0.861	0.161	0.378	**0.001**	**0.046**

Fig. 4.2(b): ALL SITES (ICD-10 : C00-C96) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

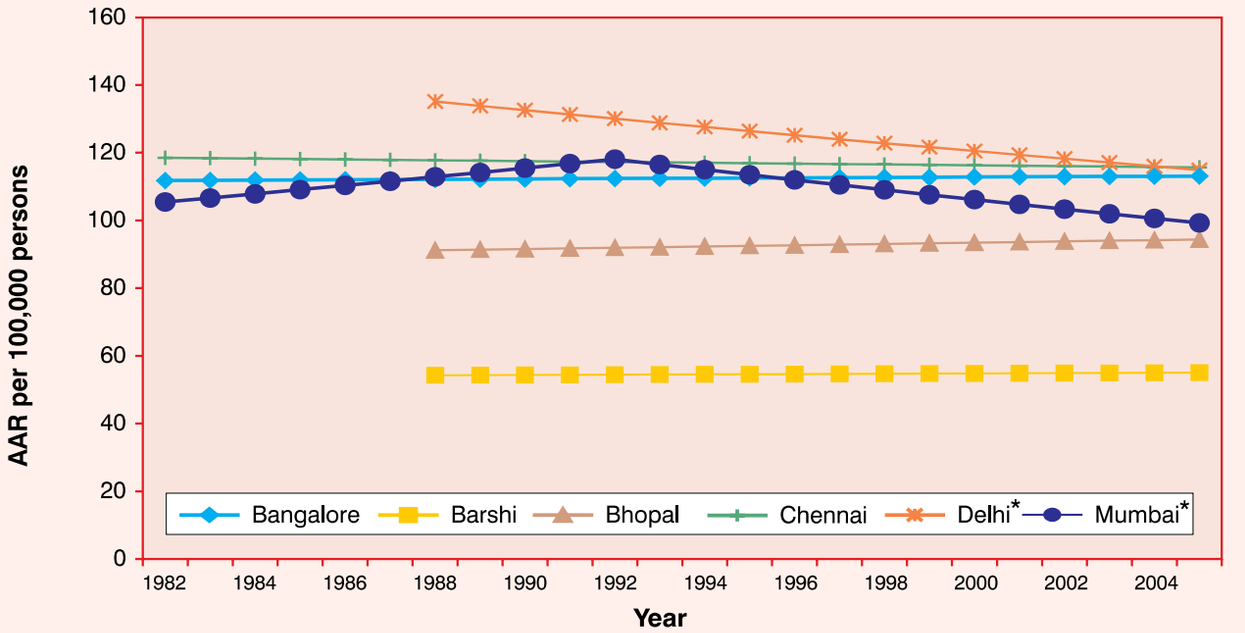


Table 4.2(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Barshi	Bhopal	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*	JP0*	JP1*
1982	111.8			118.5		105.4
1983	111.8			118.4		106.6
1984	111.9			118.2		107.9
1985	112.0			118.1		109.1
1986	112.0			118.0		110.3
1987	112.1			117.9		111.6
1988	112.1	54.3	91.2	117.7	135.2	112.9
1989	112.2	54.3	91.4	117.6	133.9	114.2
1990	112.2	54.4	91.6	117.5	132.6	115.5
1991	112.3	54.4	91.8	117.4	131.3	116.8
1992	112.4	54.5	92.0	117.2	130.1	**118.1**
1993	112.4	54.5	92.1	117.1	128.8	116.5
1994	112.5	54.6	92.3	117.0	127.6	115.0
1995	112.5	54.6	92.5	116.9	126.4	113.5
1996	112.6	54.7	92.7	116.8	125.2	112.0
1997	112.6	54.7	92.9	116.6	124.0	110.5
1998	112.7	54.8	93.1	116.5	122.8	109.0
1999	112.8	54.8	93.3	116.4	121.7	107.6
2000	112.8	54.9	93.5	116.3	120.5	106.1
2001	112.9	54.9	93.6	116.1	119.4	104.7
2002	112.9	55.0	93.8	116.0	118.2	103.4
2003	113.0	55.0	94.0	115.9	117.1	102.0
2004	113.0	55.1	94.2	115.8	116.0	100.6
2005	113.1	55.1	94.4	115.7	114.9	99.3
APC0	0.05	0.09	0.20	-0.10	**-0.95***	**-0.33***
APC1	–	–	–	–	–	**1.14***
APC2	–	–	–	–	–	**-1.33***

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.3(a): TONGUE (ICD-10 : C01-C02) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

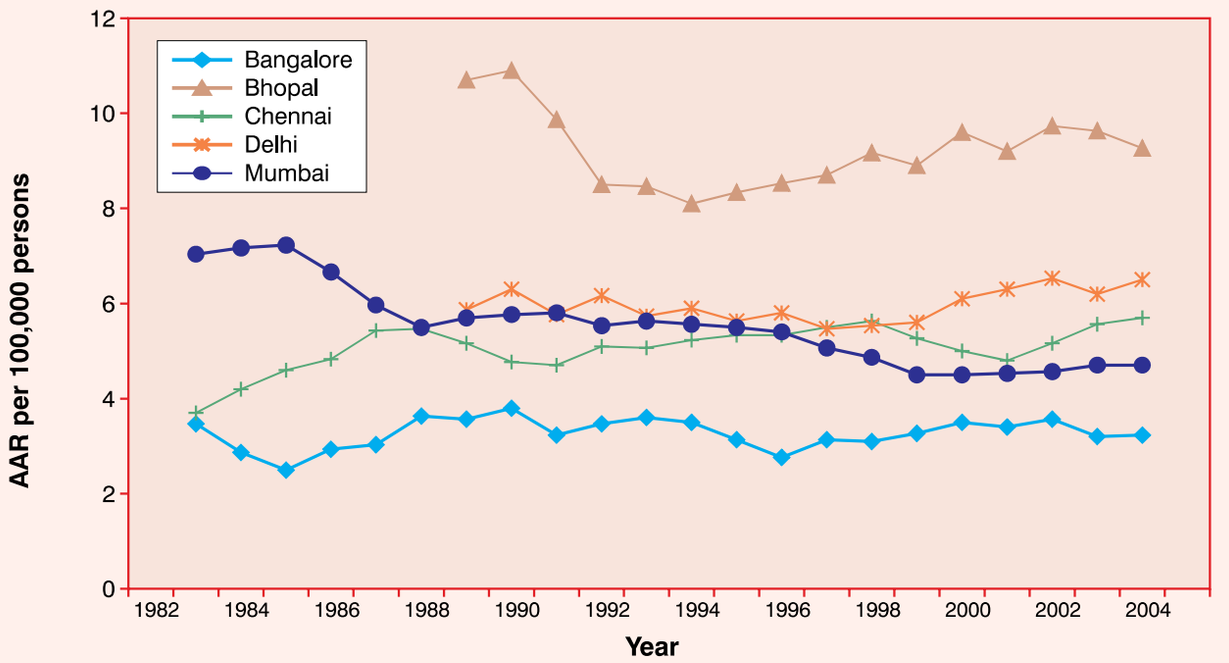


Table 4.3(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	4.1		3.7		6.9
1983	3.6		3.4		6.9
1984	2.7		4.0		7.3
1985	2.3		5.2		7.3
1986	2.5		4.6		7.1
1987	4.0		4.7		5.6
1988	2.6	8.1	7.0	4.9	5.2
1989	4.3	11.9	4.7	7.3	5.7
1990	3.8	12.1	3.8	5.4	6.2
1991	3.3	8.7	5.8	6.2	5.4
1992	2.6	8.8	4.5	5.7	5.8
1993	4.5	8.0	5.0	6.6	5.4
1994	3.7	8.6	5.7	4.9	5.7
1995	2.3	7.7	5.0	6.2	5.6
1996	3.4	8.7	5.3	5.8	5.2
1997	2.6	9.2	5.7	5.4	5.4
1998	3.4	8.2	5.5	5.2	4.6
1999	3.3	10.1	5.7	6.0	4.6
2000	3.1	8.4	4.6	5.6	4.3
2001	4.1	10.3	4.7	6.7	4.6
2002	3.0	8.9	5.1	6.6	4.7
2003	3.6	10.0	5.7	6.3	4.4
2004	3.0	10.0	5.9	5.7	5.0
2005	3.1	7.8	5.5	7.5	4.7
Slope(b)	**0.001**	**-0.035**	**0.056**	**0.043**	**-0.116**
p-value	0.988	0.567	0.018	0.218	**0.001**

Fig. 4.3(b): TONGUE (ICD-10 : C01-C02) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

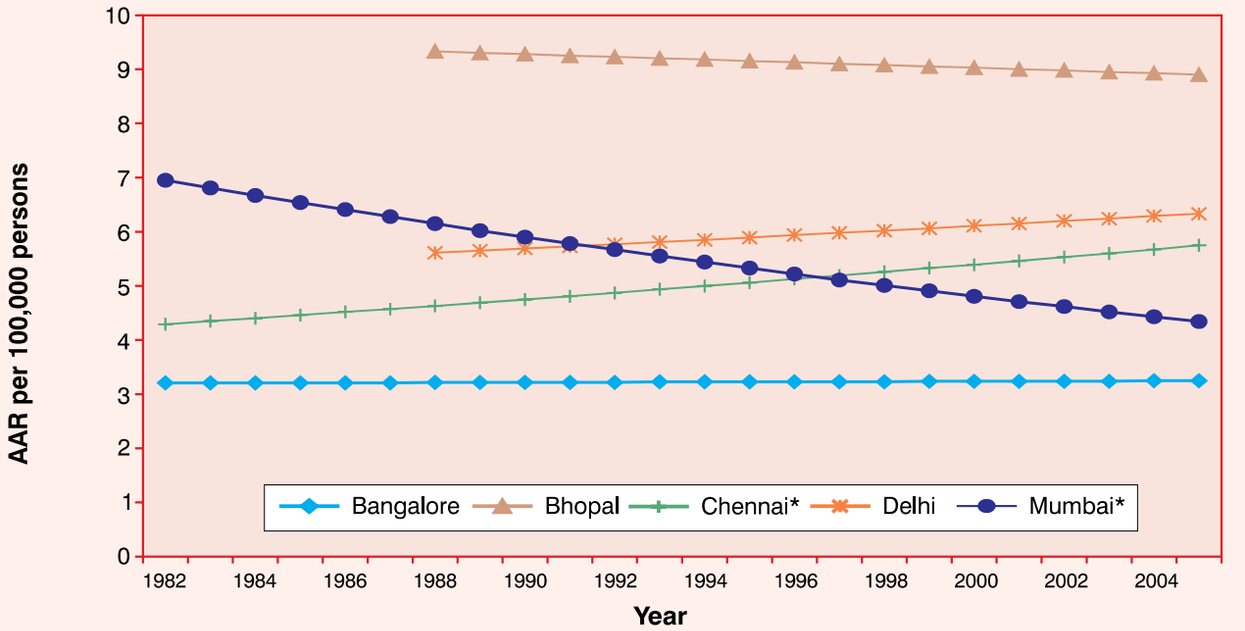


Table 4.3(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*	JP0*
1982	3.2		4.3		7.0
1983	3.2		4.4		6.8
1984	3.2		4.4		6.7
1985	3.2		4.5		6.5
1986	3.2		4.5		6.4
1987	3.2		4.6		6.3
1988	3.2	9.3	4.6	5.6	6.2
1989	3.2	9.3	4.7	5.7	6.0
1990	3.2	9.3	4.8	5.7	5.9
1991	3.2	9.3	4.8	5.7	5.8
1992	3.2	9.2	4.9	5.8	5.7
1993	3.2	9.2	4.9	5.8	5.6
1994	3.2	9.2	5.0	5.9	5.4
1995	3.2	9.2	5.1	5.9	5.3
1996	3.2	9.1	5.1	5.9	5.2
1997	3.2	9.1	5.2	6.0	5.1
1998	3.2	9.1	5.3	6.0	5.0
1999	3.2	9.1	5.3	6.1	4.9
2000	3.2	9.0	5.4	6.1	4.8
2001	3.2	9.0	5.5	6.2	4.7
2002	3.2	9.0	5.5	6.2	4.6
2003	3.2	9.0	5.6	6.2	4.5
2004	3.3	8.9	5.7	6.3	4.4
2005	3.3	8.9	5.8	6.3	4.3
APC0	0.06	-0.28	**1.27***	0.72	**-2.03***
APC1	–	–	–	–	–
APC2	–	–	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC (p<0.05) values.*

Fig. 4.4(a): MOUTH (ICD-10 : C03-C06) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

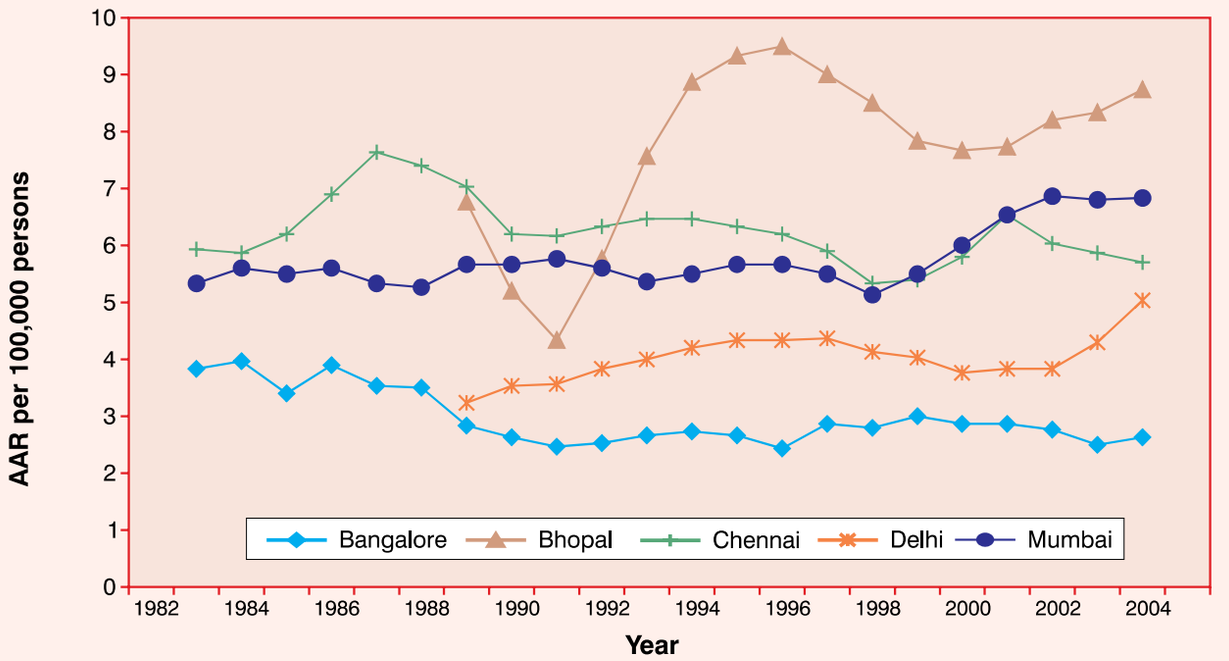


Table 4.4(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	3.7		6.4		5.6
1983	4.5		6.0		5.7
1984	3.3		5.4		4.7
1985	4.1		6.2		6.4
1986	2.8		7.0		5.4
1987	4.8		7.5		5.0
1988	3.0	8.0	8.4	3.0	5.6
1989	2.7	9.1	6.3	3.5	5.2
1990	2.8	3.2	6.4	3.2	6.2
1991	2.4	3.3	5.9	3.9	5.6
1992	2.2	6.5	6.2	3.6	5.5
1993	3.0	7.5	6.9	4.0	5.7
1994	2.8	8.7	6.3	4.4	4.9
1995	2.4	10.4	6.2	4.2	5.9
1996	2.8	8.9	6.5	4.4	6.2
1997	2.1	9.2	5.9	4.4	4.9
1998	3.7	8.9	5.3	4.3	5.4
1999	2.6	7.4	4.8	3.7	5.1
2000	2.7	7.2	6.1	4.1	6.0
2001	3.3	8.4	6.5	3.5	6.9
2002	2.6	7.6	7.0	3.9	6.7
2003	2.4	8.6	4.6	4.1	7.0
2004	2.5	8.8	6.0	4.9	6.7
2005	3.0	8.8	6.5	6.1	6.8
Slope(b)	**-0.052**	**0.135**	**-0.032**	**0.085**	**0.054**
p-value	**0.008**	0.118	0.175	**0.003**	**0.005**

Fig. 4.4(b): MOUTH (ICD-10 : C03-C06) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

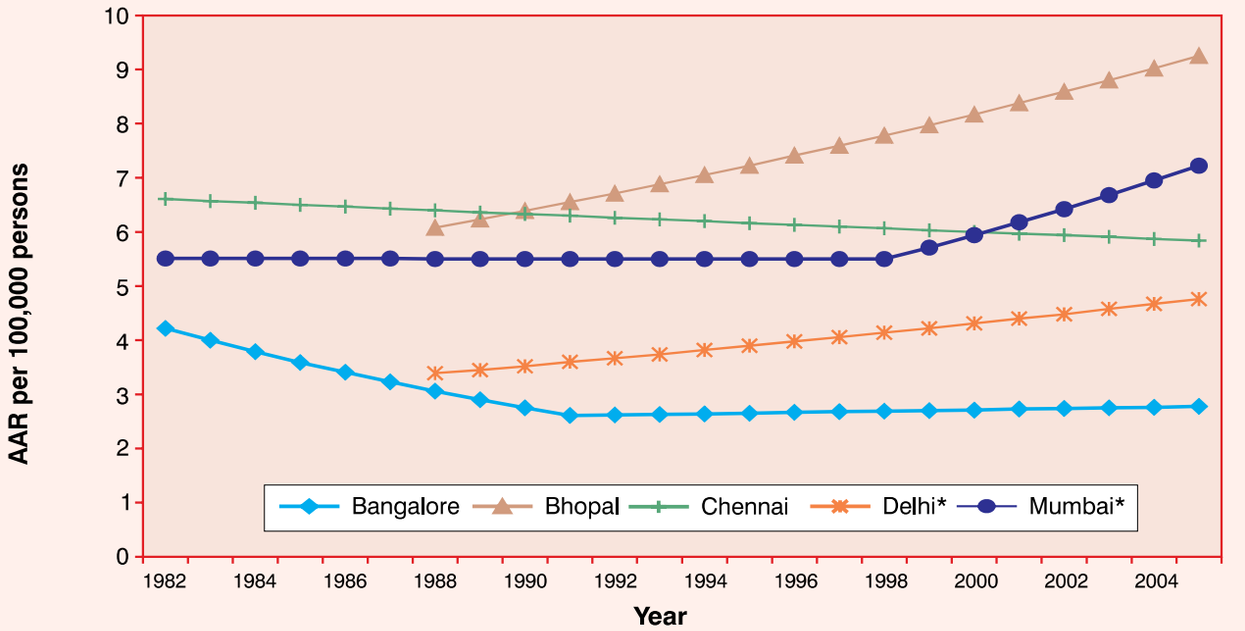


Table 4.4(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP1*	**JP0***	**JP0***	**JP0***	**JP1***
1982	4.2		6.6		5.5
1983	4.0		6.6		5.5
1984	3.8		6.5		5.5
1985	3.6		6.5		5.5
1986	3.4		6.5		5.5
1987	3.2		6.4		5.5
1988	3.1	6.1	6.4	3.4	5.5
1989	2.9	6.2	6.4	3.5	5.5
1990	2.8	6.4	6.3	3.5	5.5
1991	**2.6**	6.6	6.3	3.6	5.5
1992	2.6	6.7	6.3	3.7	5.5
1993	2.6	6.9	6.2	3.7	5.5
1994	2.6	7.1	6.2	3.8	5.5
1995	2.7	7.2	6.2	3.9	5.5
1996	2.7	7.4	6.1	4.0	5.5
1997	2.7	7.6	6.1	4.1	5.5
1998	2.7	7.8	6.1	4.1	**5.5**
1999	2.7	8.0	6.0	4.2	5.7
2000	2.7	8.2	6.0	4.3	5.9
2001	2.7	8.4	6.0	4.4	6.2
2002	2.7	8.6	5.9	4.5	6.4
2003	2.8	8.8	5.9	4.6	6.7
2004	2.8	9.0	5.9	4.7	7.0
2005	2.8	9.3	5.8	4.8	7.2
APC0	**-1.54***	2.5	-0.53	**2.03***	**0.89***
APC1	**-5.21***	–	–	–	-0.02
APC2	0.45	–	–	–	**3.98***

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.5(a): MOUTH (ICD-10 : C03-C06) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

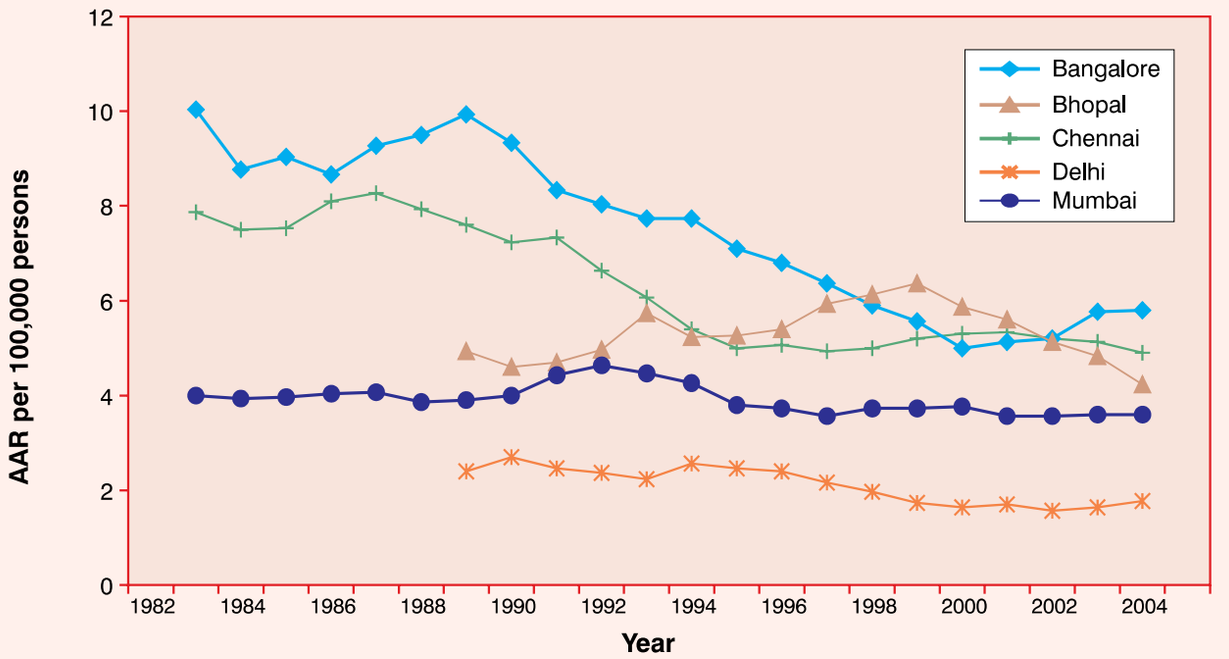


Table 4.5(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	12.2		8.4		4.3
1983	8.7		8.1		4.0
1984	9.2		7.1		3.7
1985	8.4		7.3		4.1
1986	9.5		8.2		4.1
1987	8.1		8.8		3.9
1988	10.2	4.3	7.8	2.2	4.2
1989	10.2	6.0	7.2	2.3	3.5
1990	9.4	4.5	7.8	2.7	4.0
1991	8.4	3.3	6.7	3.1	4.5
1992	7.2	6.3	7.5	1.6	4.8
1993	8.5	5.3	5.7	2.4	4.6
1994	7.5	5.6	5.0	2.7	4.0
1995	7.2	4.8	5.5	2.6	4.2
1996	6.6	5.4	4.5	2.1	3.2
1997	6.6	6.0	5.2	2.5	3.8
1998	5.9	6.4	5.1	1.9	3.7
1999	5.2	6.0	4.7	1.5	3.7
2000	5.6	6.7	5.8	1.8	3.8
2001	4.2	4.9	5.4	1.6	3.8
2002	5.6	5.2	4.8	1.7	3.1
2003	5.8	5.3	5.4	1.4	3.8
2004	5.9	4.0	5.2	1.8	3.9
2005	5.7	3.4	4.1	2.1	3.1
Slope(b)	**-0.242**	**-0.008**	**-0.176**	**-0.056**	**-0.028**
p-value	**0.001**	0.87	**0.001**	**0.006**	**0.022**

Fig. 4.5(b): MOUTH (ICD-10 : C03-C06) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

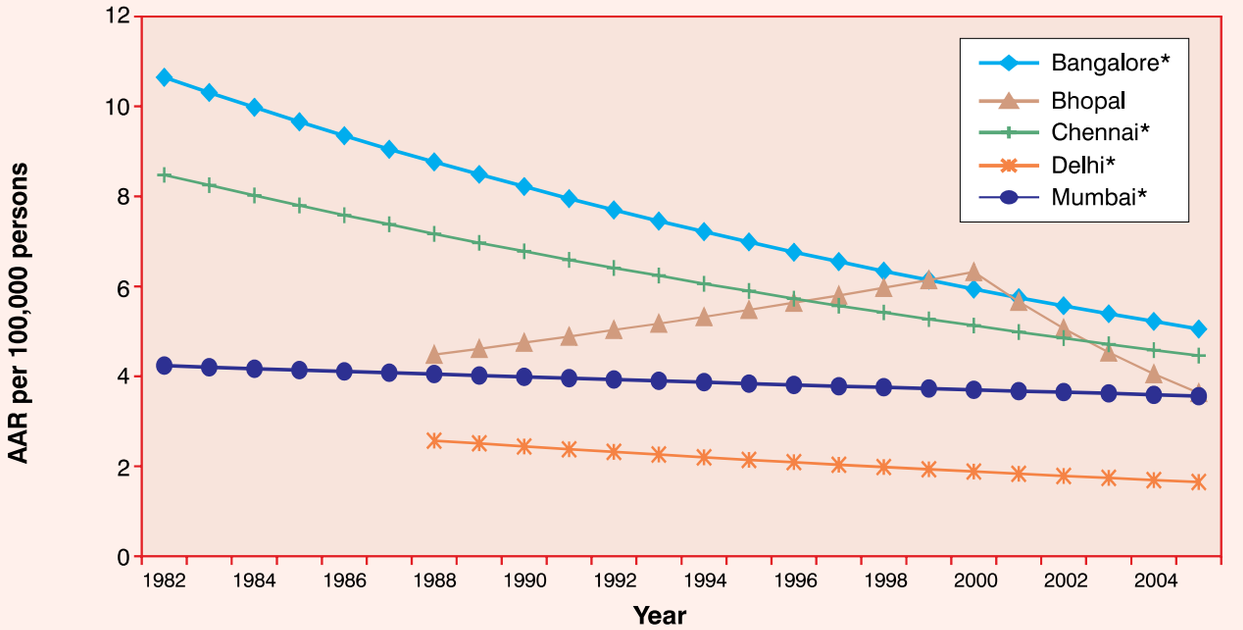


Table 4.5(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	**JP1***	**JP0***	**JP0***	**JP0***
1982	10.7		8.5		4.2
1983	10.3		8.3		4.2
1984	10.0		8.0		4.2
1985	9.7		7.8		4.1
1986	9.4		7.6		4.1
1987	9.1		7.4		4.1
1988	8.8	4.5	7.2	2.6	4.1
1989	8.5	4.6	7.0	2.5	4.0
1990	8.2	4.8	6.8	2.4	4.0
1991	8.0	4.9	6.6	2.4	4.0
1992	7.7	5.0	6.4	2.3	3.9
1993	7.5	5.2	6.2	2.3	3.9
1994	7.2	5.3	6.1	2.2	3.9
1995	7.0	5.5	5.9	2.1	3.8
1996	6.8	5.6	5.7	2.1	3.8
1997	6.6	5.8	5.6	2.0	3.8
1998	6.3	6.0	5.4	2.0	3.8
1999	6.1	6.1	5.3	1.9	3.7
2000	5.9	**6.3**	5.1	1.9	3.7
2001	5.8	5.7	5.0	1.8	3.7
2002	5.6	5.1	4.9	1.8	3.7
2003	5.4	4.5	4.7	1.7	3.6
2004	5.2	4.1	4.6	1.7	3.6
2005	5.1	3.6	4.5	1.7	3.6
APC0	**-3.19***	-0.23	**-2.76***	**-2.58***	**-0.75***
APC1	–	2.91	–	–	–
APC2	–	-10.51	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.6(a): HYPOPHARYNX (ICD-10 : C12-C13) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

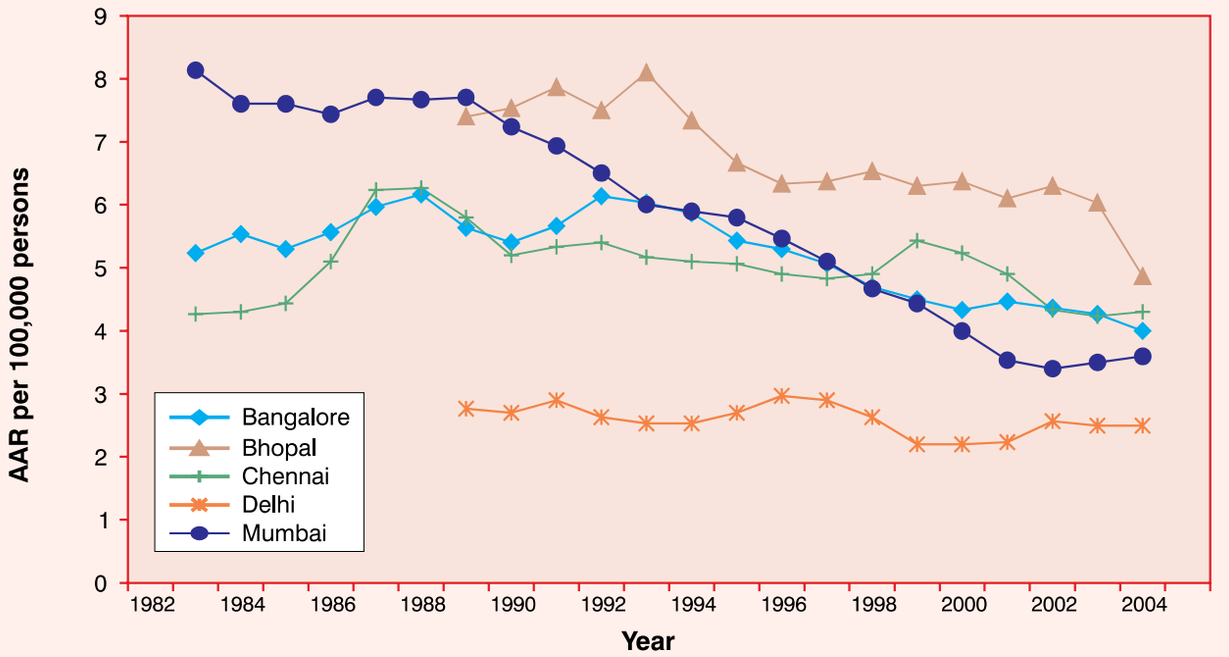


Table 4.6(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	4.4		3.5		9.1
1983	5.4		5.2		7.3
1984	5.9		4.1		8.0
1985	5.3		3.6		7.5
1986	4.7		5.6		7.3
1987	6.7		6.1		7.5
1988	6.5	5.2	7.0	2.9	8.3
1989	5.3	7.6	5.7	2.1	7.2
1990	5.1	9.4	4.7	3.3	7.6
1991	5.8	5.6	5.2	2.7	6.9
1992	6.1	8.6	6.1	2.7	6.3
1993	6.5	8.3	4.9	2.5	6.3
1994	5.5	7.4	4.5	2.4	5.4
1995	5.6	6.3	5.9	2.7	6.0
1996	5.2	6.3	4.8	3.0	6.0
1997	5.1	6.4	4.0	3.2	4.4
1998	4.9	6.4	5.7	2.5	4.9
1999	4.1	6.8	5.0	2.2	4.7
2000	4.5	5.7	5.6	1.9	3.7
2001	4.4	6.6	5.1	2.5	3.6
2002	4.5	6.0	4.0	2.3	3.3
2003	4.2	6.3	3.9	2.9	3.3
2004	4.1	5.8	4.8	2.3	3.9
2005	3.7	2.5	4.2	2.3	3.6
Slope(b)	**-0.068**	**-0.152**	**-0.015**	**-0.024**	**-0.240**
p-value	**0.003**	**0.020**	0.586	0.177	**0.001**

Fig. 4.6(b): HYPOPHARYNX (ICD-10 : C12-C13) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

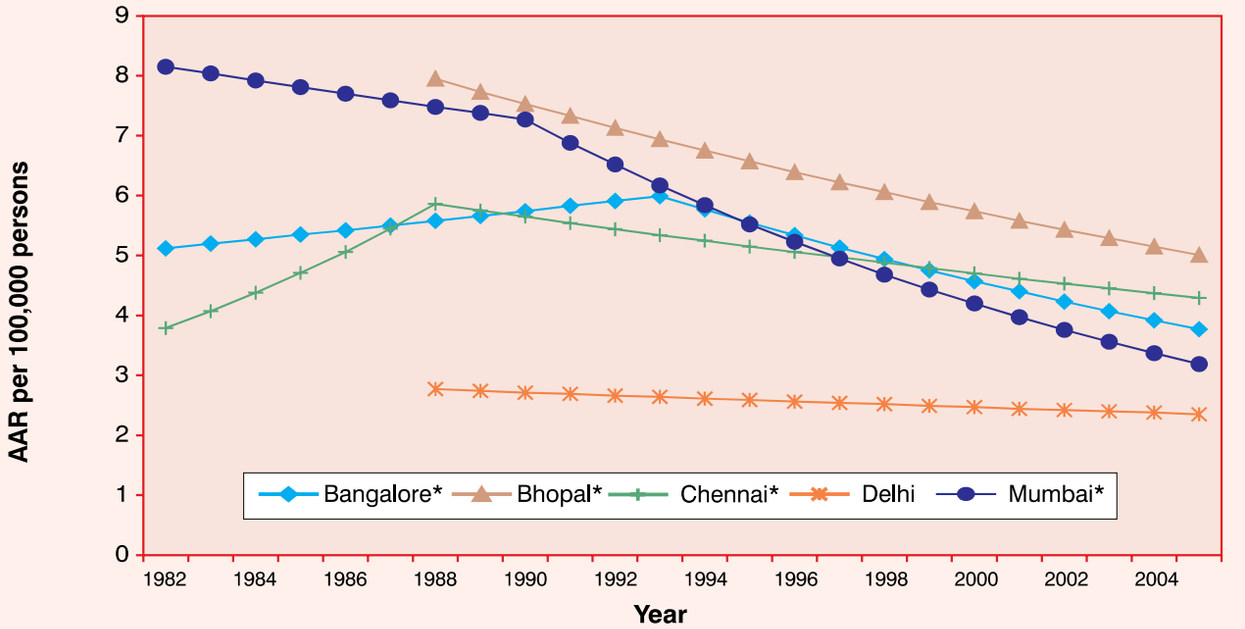


Table 4.6(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP1*	**JP0***	**JP1***	**JP0***	**JP1***
1982	5.1		3.8		8.2
1983	5.2		4.1		8.0
1984	5.3		4.4		7.9
1985	5.4		4.7		7.8
1986	5.4		5.1		7.7
1987	5.5		5.5		7.6
1988	5.6	8.0	**5.9**	2.8	7.5
1989	5.7	7.7	5.8	2.7	7.4
1990	5.7	7.5	5.7	2.7	**7.3**
1991	5.8	7.3	5.5	2.7	6.9
1992	5.9	7.1	5.4	2.7	6.5
1993	**6.0**	6.9	5.3	2.6	6.2
1994	5.8	6.8	5.3	2.6	5.8
1995	5.6	6.6	5.2	2.6	5.5
1996	5.3	6.4	5.1	2.6	5.2
1997	5.1	6.2	5.0	2.5	5.0
1998	4.9	6.1	4.9	2.5	4.7
1999	4.8	5.9	4.8	2.5	4.4
2000	4.6	5.7	4.7	2.5	4.2
2001	4.4	5.6	4.6	2.4	4.0
2002	4.2	5.4	4.5	2.4	3.8
2003	4.1	5.3	4.5	2.4	3.6
2004	3.9	5.2	4.4	2.4	3.4
2005	3.8	5.0	4.3	2.4	3.2
APC0	**-1.38***	**-2.68***	-0.20	-0.95	**-4.24***
APC1	1.44	–	7.55	–	-1.41
APC2	**-3.80***	–	**-1.82***	–	**-5.35***

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.7(a): OESOPHAGUS (ICD-10 : C15) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

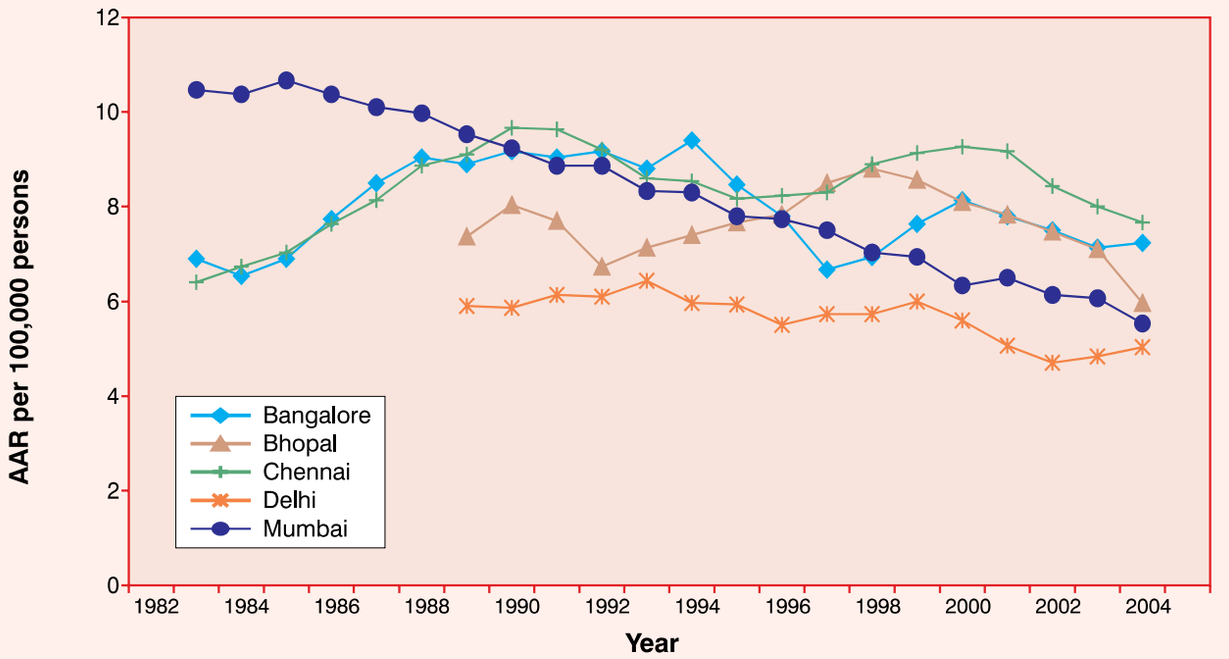


Table 4.7(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	7.6		6.2		10.9
1983	5.7		5.8		9.3
1984	7.4		7.2		11.2
1985	6.5		7.2		10.6
1986	6.8		6.7		10.2
1987	9.9		9.0		10.3
1988	8.8	5.2	8.7	5.5	9.8
1989	8.4	7.0	8.9	6.0	9.8
1990	9.5	9.9	9.7	6.2	9.0
1991	9.6	7.2	10.4	5.4	8.9
1992	8.0	6.0	8.8	6.8	8.7
1993	9.9	7.0	8.4	6.1	9.0
1994	8.5	8.4	8.6	6.4	7.3
1995	9.8	6.8	8.6	5.4	8.6
1996	7.1	7.8	7.3	6.0	7.5
1997	6.5	8.9	8.8	5.1	7.1
1998	6.4	8.8	8.8	6.1	7.9
1999	7.9	8.7	9.1	6.0	6.1
2000	8.6	8.2	9.5	5.9	6.8
2001	7.9	7.4	9.2	4.9	6.1
2002	6.9	7.9	8.8	4.4	6.6
2003	7.7	7.1	7.3	4.8	5.7
2004	6.8	6.3	7.9	5.3	5.9
2005	7.2	4.5	7.8	5.0	5.0
Slope(b)	**-0.014**	**-0.021**	**0.060**	**-0.070**	**-0.246**
p-value	0.718	0.740	0.068	**0.011**	**0.001**

Fig. 4.7(b): OESOPHAGUS (ICD-10 : C15) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

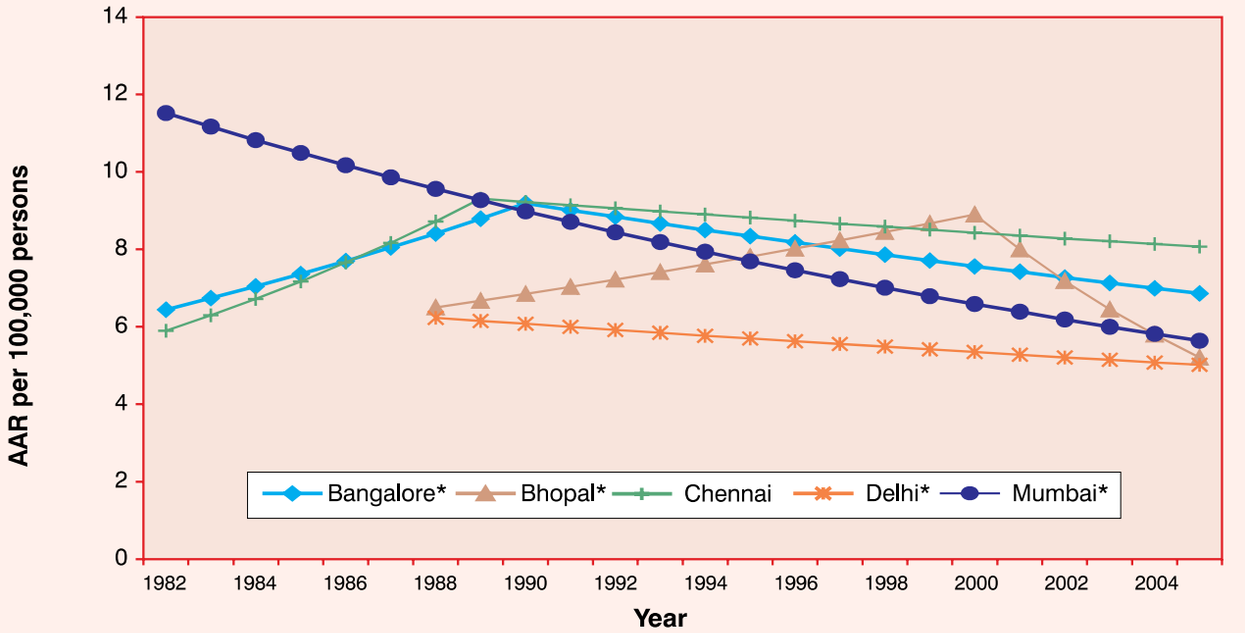


Table 4.7(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP1*	**JP1***	**JP1***	**JP0***	**JP0***
1982	6.4		5.9		11.5
1983	6.7		6.3		11.2
1984	7.0		6.7		10.8
1985	7.4		7.2		10.5
1986	7.7		7.7		10.2
1987	8.1		8.2		9.9
1988	8.4	6.5	8.7	6.2	9.6
1989	8.8	6.7	**9.3**	6.2	9.3
1990	9.2	6.9	9.2	6.1	9.0
1991	9.0	7.0	9.1	6.0	8.7
1992	8.8	7.2	9.1	5.9	8.4
1993	8.7	7.4	9.0	5.9	8.2
1994	8.5	7.6	8.9	5.8	7.9
1995	8.3	7.8	8.8	5.7	7.7
1996	8.2	8.0	8.7	5.6	7.5
1997	8.0	8.2	8.7	5.6	7.2
1998	7.9	8.5	8.6	5.5	7.0
1999	7.7	8.7	8.5	5.4	6.8
2000	7.6	**8.9**	8.4	5.4	6.6
2001	7.4	8.0	8.4	5.3	6.4
2002	7.3	7.2	8.3	5.2	6.2
2003	7.1	6.5	8.2	5.2	6.0
2004	7.0	5.8	8.1	5.1	5.8
2005	6.9	5.2	8.1	5.0	5.6
APC0	-0.12	-0.34	0.82	**-1.27***	**-3.06***
APC1	**4.54***	2.66	**6.73***	–	–
APC2	**-1.93***	**-10.17***	-0.89	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.8(a): OESOPHAGUS (ICD-10 : C15) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

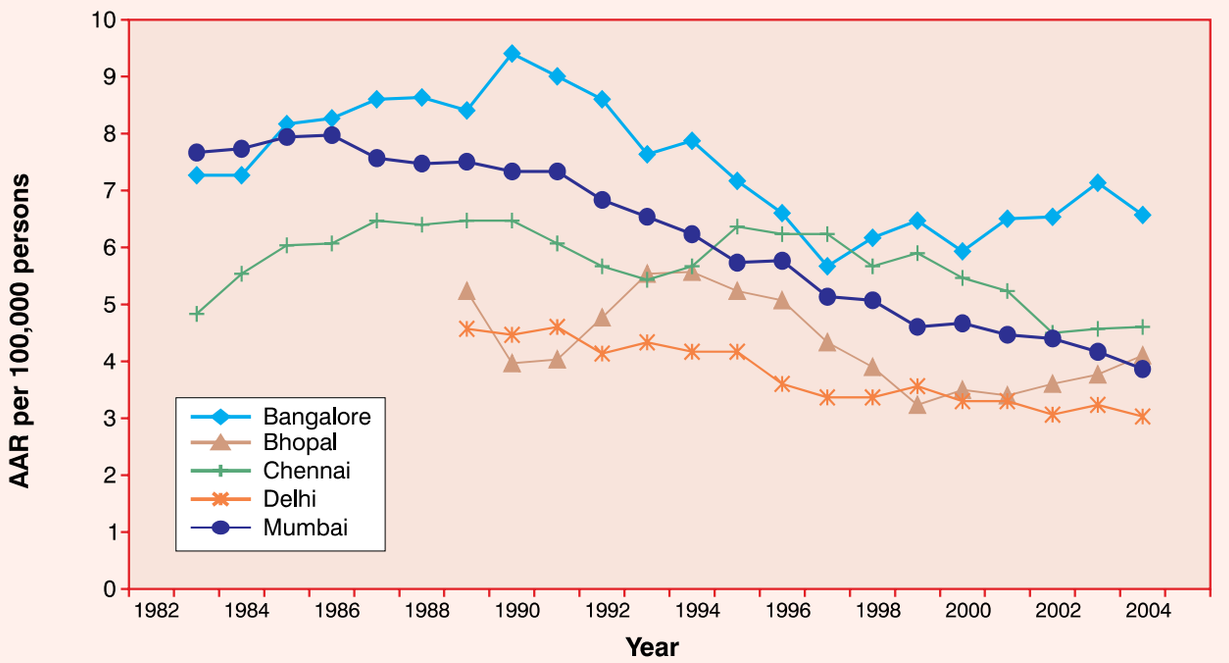


Table 4.8(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	6.5		3.2		8.1
1983	6.6		5.6		7.0
1984	8.7		5.7		7.9
1985	6.5		5.3		8.3
1986	9.3		7.1		7.6
1987	9.0		5.8		8.0
1988	7.5	7.2	6.5	4.3	7.1
1989	9.4	4.7	6.9	4.3	7.3
1990	8.3	3.8	6.0	5.1	8.1
1991	10.5	3.4	6.5	4.0	6.6
1992	8.2	4.9	5.7	4.7	7.3
1993	7.1	6.0	4.8	3.7	6.6
1994	7.6	5.7	5.8	4.6	5.7
1995	8.9	5.0	6.4	4.2	6.4
1996	5.0	5.0	6.9	3.7	5.1
1997	5.9	5.2	5.4	2.9	5.8
1998	6.1	2.8	6.4	3.5	4.5
1999	6.5	3.7	5.2	3.7	4.9
2000	6.8	3.2	6.1	3.5	4.4
2001	4.5	3.6	5.1	2.7	4.7
2002	8.2	3.4	4.5	3.7	4.3
2003	6.9	3.8	3.9	2.8	4.2
2004	6.3	4.1	5.3	3.2	4.0
2005	6.5	4.4	4.6	3.1	3.4
Slope(b)	**-0.084**	**-0.108**	**-0.029**	**-0.101**	**-0.021**
p-value	0.051	**0.029**	0.315	**0.001**	**0.001**

Fig. 4.8(b): OESOPHAGUS (ICD-10 : C15) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

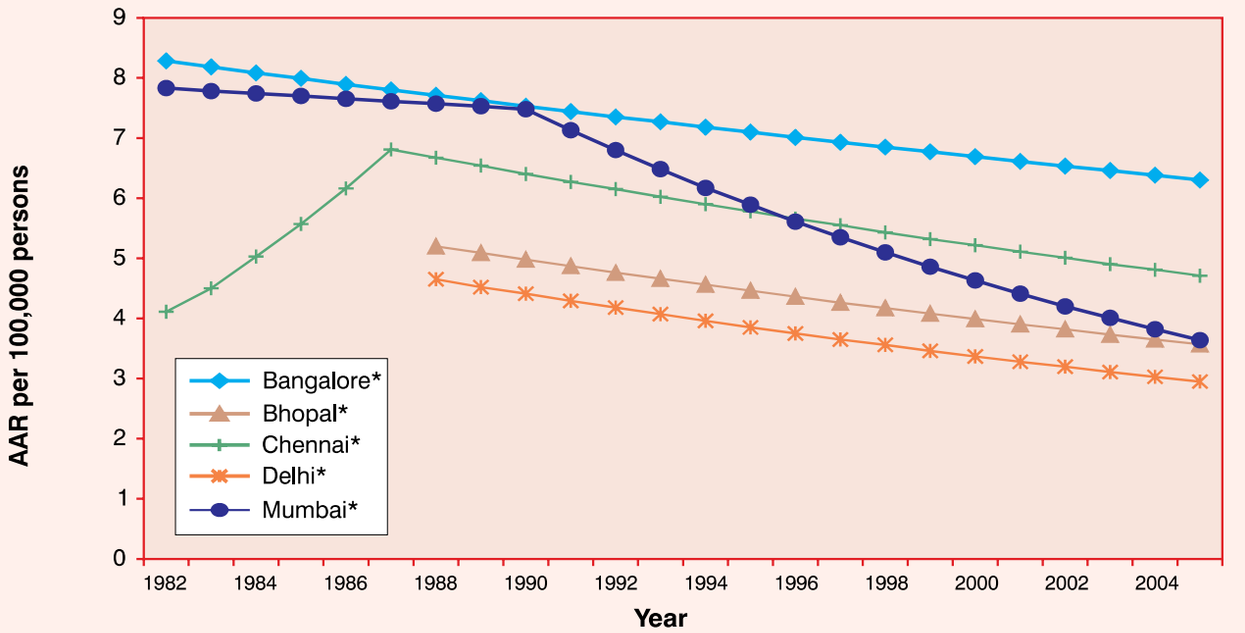


Table 4.8(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	**JP0***	**JP1***	**JP0***	**JP1***
1982	8.3		4.1		7.8
1983	8.2		4.5		7.8
1984	8.1		5.0		7.7
1985	8.0		5.6		7.7
1986	7.9		6.2		7.7
1987	7.8		**6.8**		7.6
1988	7.7	5.2	6.7	4.7	7.6
1989	7.6	5.1	6.5	4.5	7.5
1990	7.5	5.0	6.4	4.4	**7.5**
1991	7.4	4.9	6.3	4.3	7.1
1992	7.4	4.8	6.2	4.2	6.8
1993	7.3	4.7	6.0	4.1	6.5
1994	7.2	4.6	5.9	4.0	6.2
1995	7.1	4.5	5.8	3.9	5.9
1996	7.0	4.4	5.7	3.8	5.6
1997	6.9	4.3	5.6	3.7	5.4
1998	6.9	4.2	5.4	3.6	5.1
1999	6.8	4.1	5.3	3.5	4.9
2000	6.7	4.0	5.2	3.4	4.6
2001	6.6	3.9	5.1	3.3	4.4
2002	6.5	3.8	5.0	3.2	4.2
2003	6.5	3.7	4.9	3.1	4.0
2004	6.4	3.7	4.8	3.0	3.8
2005	6.3	3.6	4.7	3.0	3.6
APC0	**-1.18***	**-2.19***	-0.44	**-2.64***	**-3.52***
APC1	–	–	**10.63***	–	-0.56
APC2	–	–	**-2.03***	**–**	**-4.69***

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.9(a): STOMACH (ICD-10 : C16) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

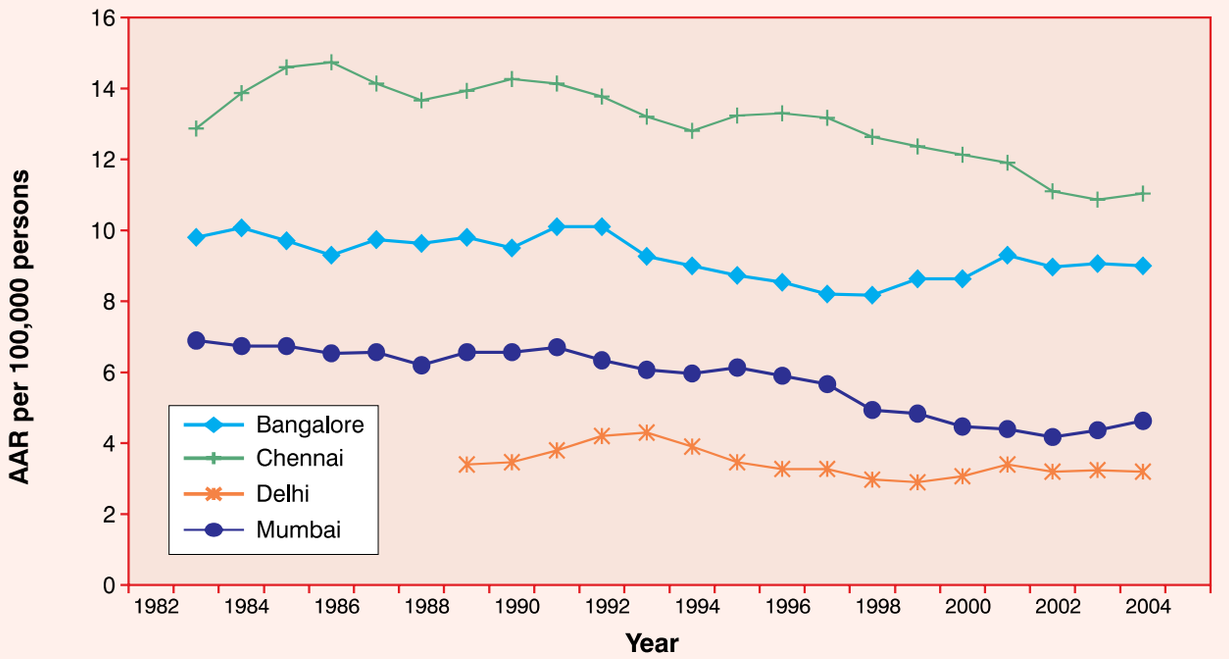


Table 4.9(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	10.0	11.8		7.1
1983	9.9	13.7		7.0
1984	9.5	13.1		6.6
1985	10.8	14.8		6.6
1986	8.8	15.9		7.0
1987	8.3	13.5		6.0
1988	12.1	13.0	3.4	6.7
1989	8.5	14.5	3.2	5.9
1990	8.8	14.3	3.6	7.1
1991	11.2	14.0	3.6	6.7
1992	10.3	14.1	4.2	6.3
1993	8.8	13.2	4.8	6.0
1994	8.7	12.3	3.9	5.9
1995	9.5	12.9	3.0	6.0
1996	8.0	14.5	3.5	6.5
1997	8.1	12.5	3.3	5.2
1998	8.5	12.5	3.0	5.3
1999	7.9	12.9	2.6	4.3
2000	9.5	11.7	3.1	4.9
2001	8.5	11.8	3.5	4.2
2002	9.9	12.2	3.6	4.1
2003	8.5	9.3	2.5	4.2
2004	8.8	11.1	3.6	4.8
2005	9.7	12.7	3.5	4.9
Slope(b)	**-0.054**	**-0.117**	**-0.034**	**-0.125**
p-value	0.089	**0.002**	0.178	**0.001**

Fig. 4.9(b): STOMACH (ICD-10 : C16) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

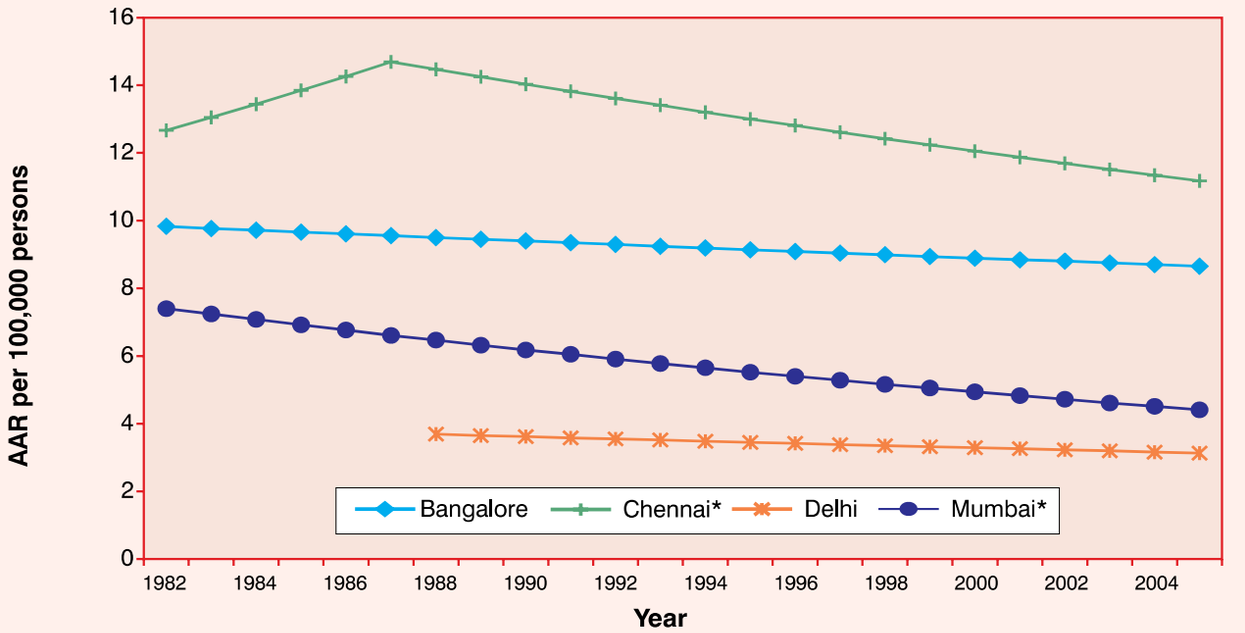


Table 4.9(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	**JP1***	**JP0***	**JP0***
1982	9.8	12.7		7.4
1983	9.8	13.1		7.2
1984	9.7	13.4		7.1
1985	9.7	13.9		6.9
1986	9.6	14.3		6.8
1987	9.6	**14.7**		6.6
1988	9.5	14.5	3.7	6.5
1989	9.5	14.3	3.7	6.3
1990	9.4	14.0	3.6	6.2
1991	9.4	13.8	3.6	6.1
1992	9.3	13.6	3.6	5.9
1993	9.2	13.4	3.5	5.8
1994	9.2	13.2	3.5	5.7
1995	9.1	13.0	3.5	5.5
1996	9.1	12.8	3.4	5.4
1997	9.0	12.6	3.4	5.3
1998	9.0	12.4	3.4	5.2
1999	8.9	12.2	3.3	5.1
2000	8.9	12.1	3.3	4.9
2001	8.8	11.9	3.3	4.8
2002	8.8	11.7	3.2	4.7
2003	8.8	11.5	3.2	4.6
2004	8.7	11.3	3.2	4.5
2005	8.7	11.2	3.1	4.4
APC0	-0.55	**-0.93***	-0.95	**-2.23***
APC1	–	3.00	–	–
APC2	–	**-1.51***	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.10(a): COLON (ICD-10 : C18) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

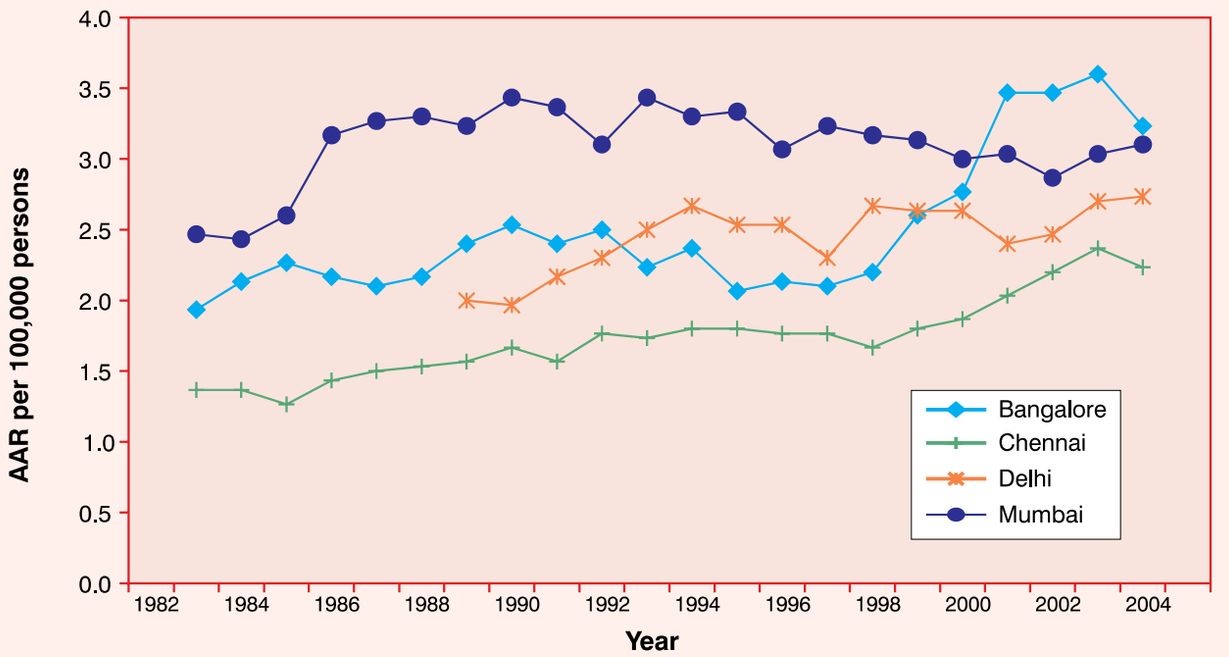


Table 4.10(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	1.8	1.4		2.4
1983	1.8	2.0		2.7
1984	2.2	0.7		2.3
1985	2.4	1.4		2.3
1986	2.2	1.7		3.2
1987	1.9	1.2		4.0
1988	2.2	1.6	2.0	2.6
1989	2.4	1.8	1.9	3.3
1990	2.6	1.3	2.1	3.8
1991	2.6	1.9	1.9	3.2
1992	2.0	1.5	2.5	3.1
1993	2.9	1.9	2.5	3.0
1994	1.8	1.8	2.5	4.2
1995	2.4	1.7	3.0	2.7
1996	2.0	1.9	2.1	3.1
1997	2.0	1.7	2.5	3.4
1998	2.3	1.7	2.3	3.2
1999	2.3	1.6	3.2	2.9
2000	3.2	2.1	2.4	3.3
2001	2.8	1.9	2.3	2.8
2002	4.4	2.1	2.5	3.0
2003	3.2	2.6	2.6	2.8
2004	3.2	2.4	3.0	3.3
2005	3.3	1.7	2.6	3.2
Slope(b)	**0.060**	**0.035**	**0.040**	**0.016**
p-value	**0.001**	**0.001**	**0.013**	0.274

Fig. 4.10(b): COLON (ICD-10 : C18) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

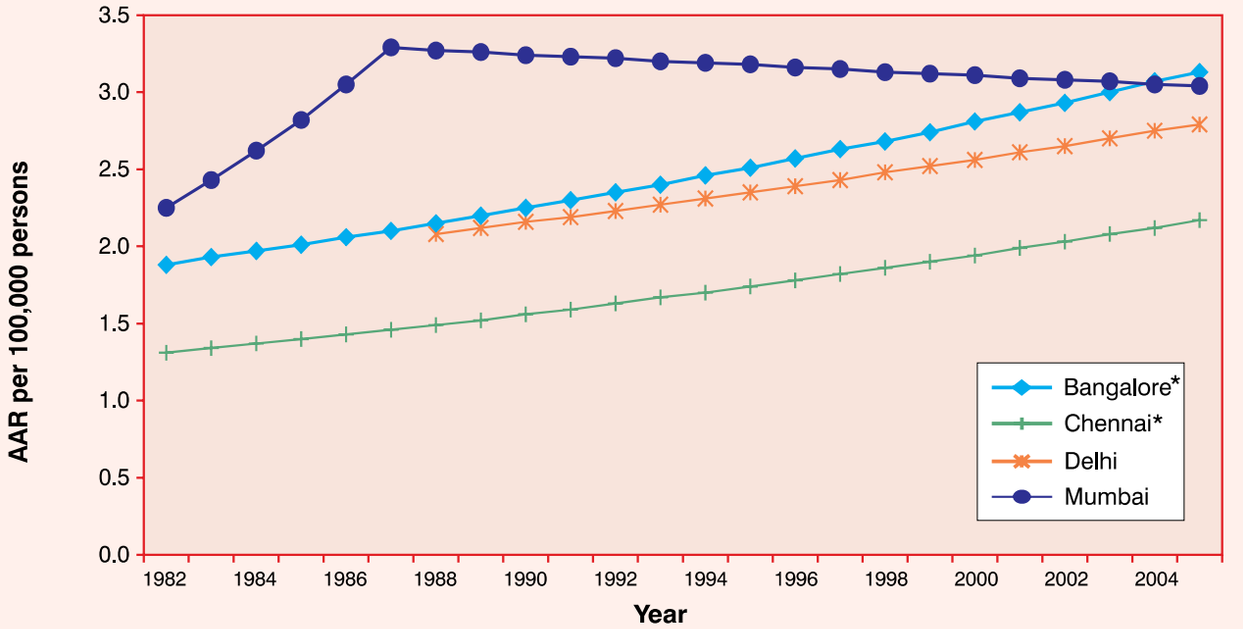


Table 4.10(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	**JP0***	**JP0***	**JP1***
1982	1.9	1.3		2.3
1983	1.9	1.3		2.4
1984	2.0	1.4		2.6
1985	2.0	1.4		2.8
1986	2.1	1.4		3.1
1987	2.1	1.5		**3.3**
1988	2.2	1.5	2.1	3.3
1989	2.2	1.5	2.1	3.3
1990	2.3	1.6	2.2	3.2
1991	2.3	1.6	2.2	3.2
1992	2.4	1.6	2.2	3.2
1993	2.4	1.7	2.3	3.2
1994	2.5	1.7	2.3	3.2
1995	2.5	1.7	2.4	3.2
1996	2.6	1.8	2.4	3.2
1997	2.6	1.8	2.4	3.2
1998	2.7	1.9	2.5	3.1
1999	2.7	1.9	2.5	3.1
2000	2.8	1.9	2.6	3.1
2001	2.9	2.0	2.6	3.1
2002	2.9	2.0	2.7	3.1
2003	3.0	2.1	2.7	3.1
2004	3.1	2.1	2.8	3.1
2005	3.1	2.2	2.8	3.0
APC0	**2.24***	**2.23***	**1.74***	0.63
APC1	–	–	–	7.88
APC2	–	–	–	-0.43

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.11(a): RECTUM (ICD-10 : C19-C20) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

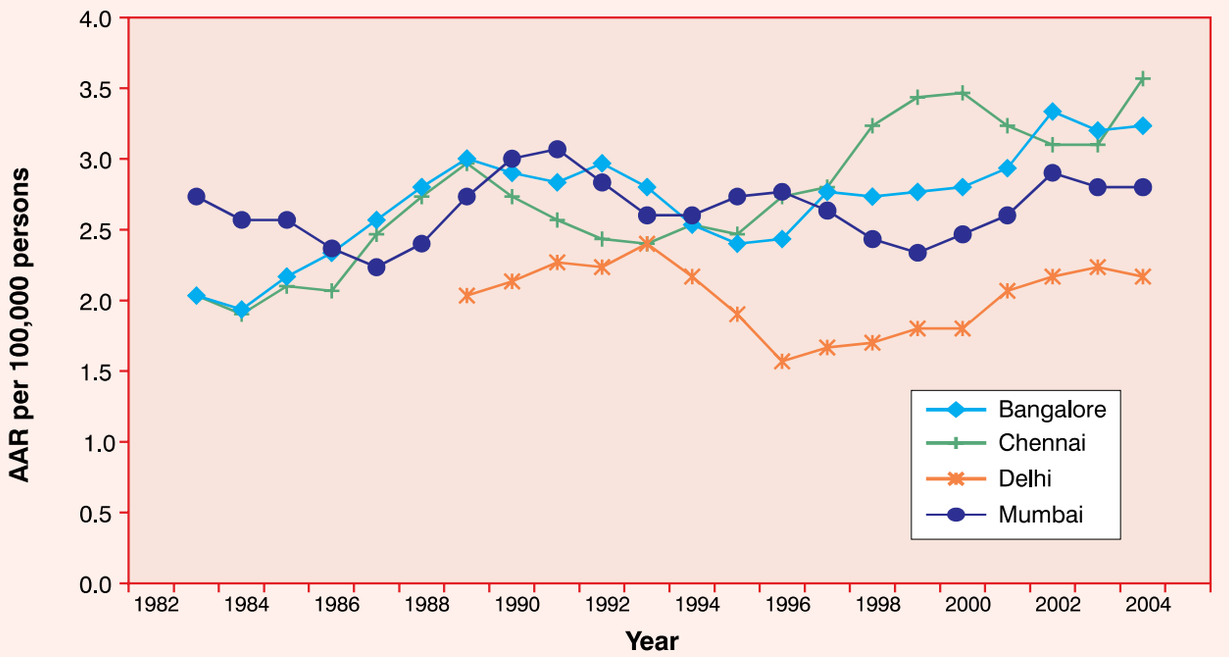


Table 4.11(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	2.5	2.2		3.1
1983	1.8	1.8		2.2
1984	1.8	2.1		2.9
1985	2.2	1.8		2.6
1986	2.5	2.4		2.2
1987	2.3	2.0		2.3
1988	2.9	3.0	1.8	2.2
1989	3.2	3.2	1.9	2.7
1990	2.9	2.7	2.4	3.3
1991	2.6	2.3	2.1	3.0
1992	3.0	2.7	2.3	2.9
1993	3.3	2.3	2.3	2.6
1994	2.1	2.2	2.6	2.3
1995	2.2	3.1	1.6	2.9
1996	2.9	2.1	1.5	3.0
1997	2.2	3.0	1.6	2.4
1998	3.2	3.3	1.9	2.5
1999	2.8	3.4	1.6	2.4
2000	2.3	3.6	1.9	2.1
2001	3.3	3.4	1.9	2.9
2002	3.2	2.7	2.4	2.8
2003	3.5	3.2	2.2	3.0
2004	2.9	3.4	2.1	2.6
2005	3.3	4.1	2.2	2.8
Slope(b)	**0.040**	**0.069**	**-0.001**	**0.004**
p-value	**0.004**	**0.001**	0.973	0.718

Fig. 4.11(b): RECTUM (ICD-10 : C19-C20) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

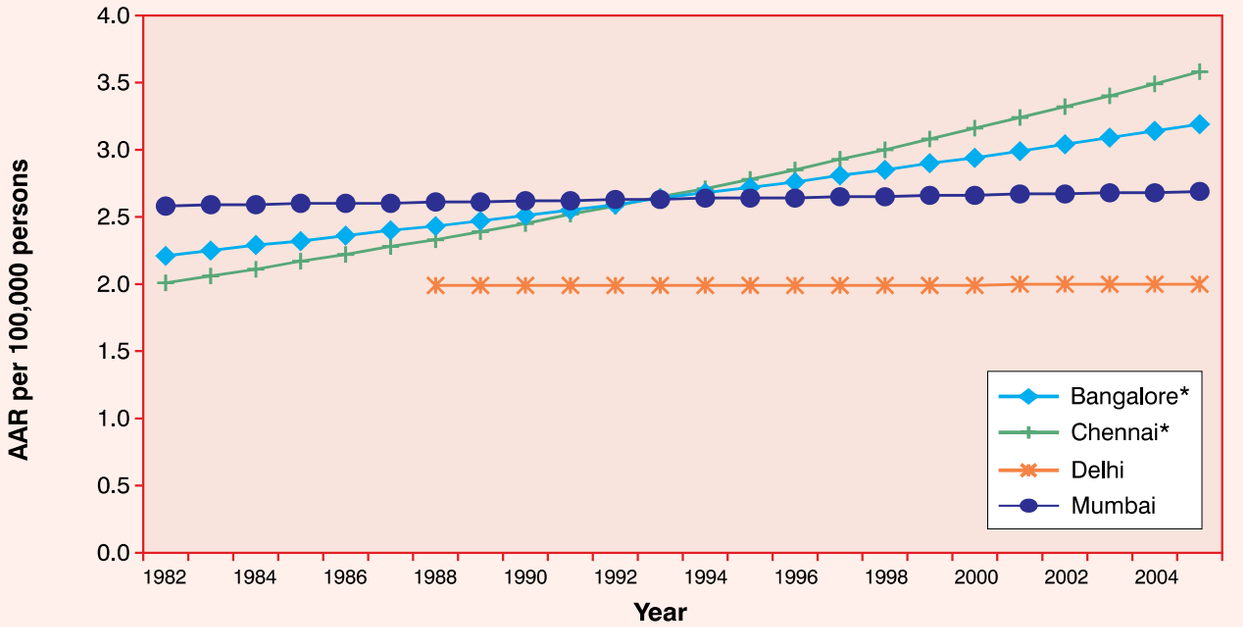


Table 4.11(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*
1982	2.2	2.0		2.6
1983	2.3	2.1		2.6
1984	2.3	2.1		2.6
1985	2.3	2.2		2.6
1986	2.4	2.2		2.6
1987	2.4	2.3		2.6
1988	2.4	2.3	2.0	2.6
1989	2.5	2.4	2.0	2.6
1990	2.5	2.5	2.0	2.6
1991	2.6	2.5	2.0	2.6
1992	2.6	2.6	2.0	2.6
1993	2.6	2.7	2.0	2.6
1994	2.7	2.7	2.0	2.6
1995	2.7	2.8	2.0	2.6
1996	2.8	2.9	2.0	2.6
1997	2.8	2.9	2.0	2.7
1998	2.9	3.0	2.0	2.7
1999	2.9	3.1	2.0	2.7
2000	2.9	3.2	2.0	2.7
2001	3.0	3.2	2.0	2.7
2002	3.0	3.3	2.0	2.7
2003	3.1	3.4	2.0	2.7
2004	3.1	3.5	2.0	2.7
2005	3.2	3.6	2.0	2.7
APC0	1.60*	2.54*	0.04	0.00
APC1	–	–	–	0.17
APC2	–	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.12(a): LIVER (ICD-10 : C22) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

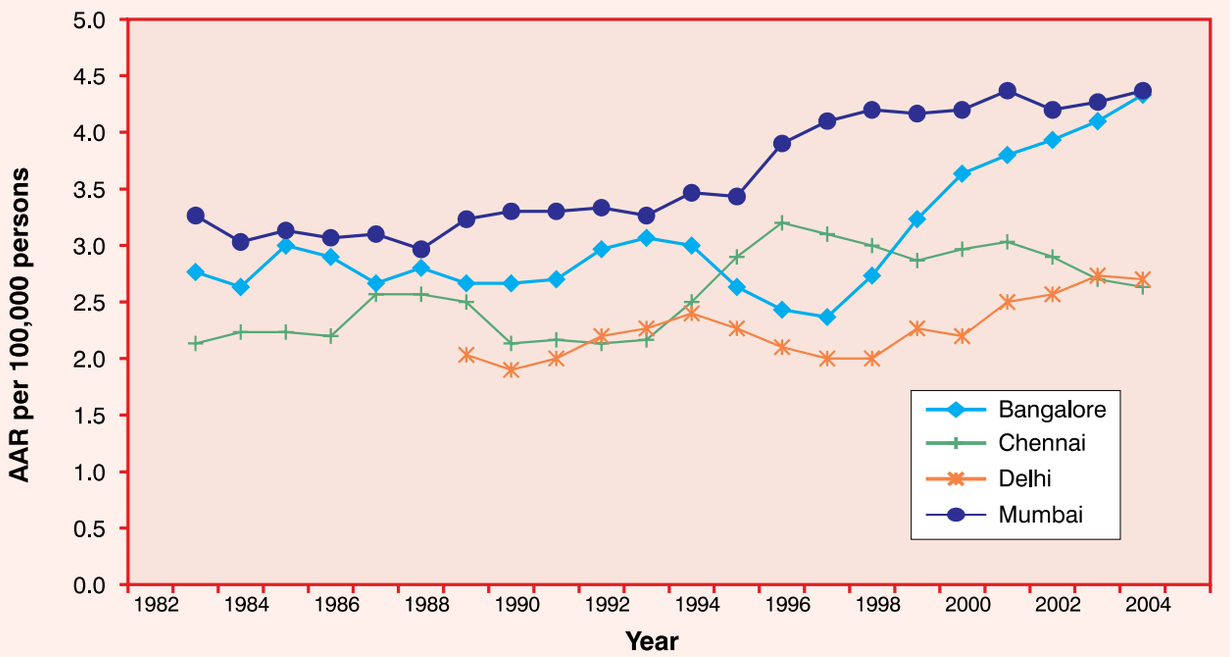


Table 4.12(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	3.6	1.8		3.7
1983	1.4	1.4		3.1
1984	3.3	2.4		3.0
1985	3.2	2.3		3.0
1986	2.5	1.9		3.4
1987	3.0	2.3		2.8
1988	2.5	3.4	2.3	3.1
1989	2.9	1.6	2.0	3.0
1990	2.6	2.1	1.8	3.6
1991	2.5	2.3	1.9	3.3
1992	3.0	2.0	2.3	3.0
1993	3.4	1.6	2.4	3.7
1994	2.8	2.4	2.1	3.1
1995	2.8	3.0	2.7	3.6
1996	2.3	3.2	2.0	3.6
1997	2.2	3.3	1.6	4.5
1998	2.6	2.8	2.4	4.2
1999	3.4	2.9	2.0	3.9
2000	3.7	2.9	2.4	4.4
2001	3.8	3.1	2.2	4.3
2002	3.9	3.0	2.9	4.4
2003	4.1	2.5	2.6	3.9
2004	4.3	2.5	2.7	4.5
2005	4.6	2.9	2.8	4.7
Slope(b)	**0.061**	**0.048**	**0.039**	**0.068**
p-value	**0.003**	**0.002**	**0.011**	**0.001**

Fig. 4.12(b): LIVER (ICD-10 : C22) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

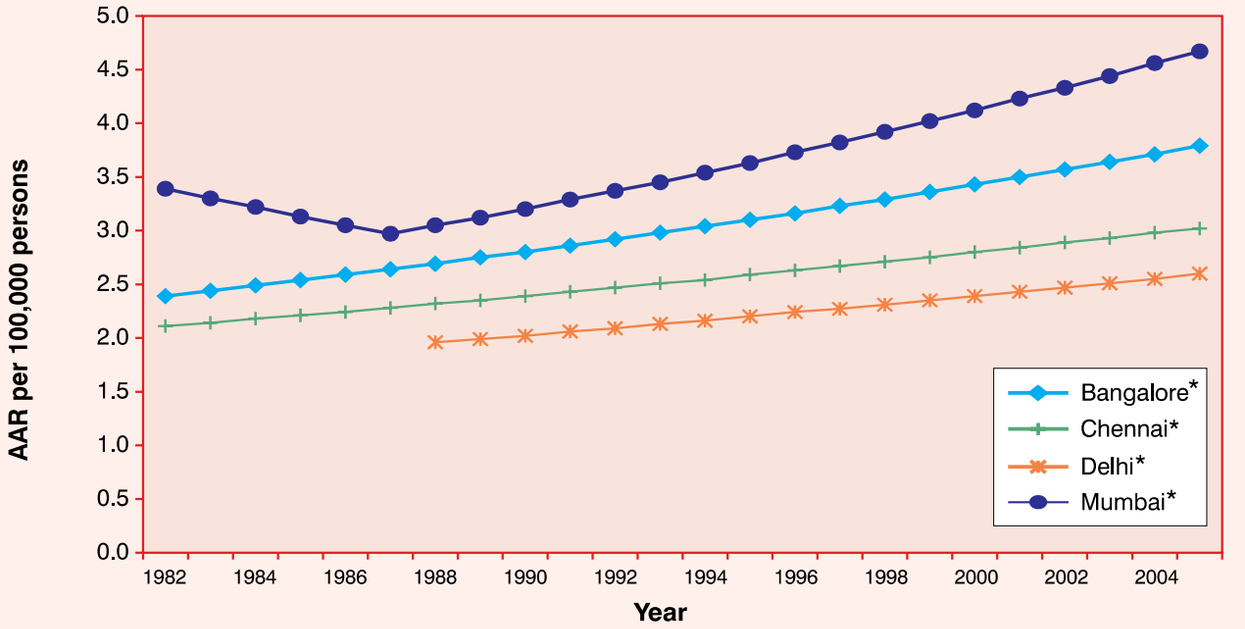


Table 4.12(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	**JP0***	**JP0***	**JP1***
1982	2.4	2.1		3.4
1983	2.4	2.1		3.3
1984	2.5	2.2		3.2
1985	2.5	2.2		3.1
1986	2.6	2.2		3.1
1987	2.6	2.3		**3.0**
1988	2.7	2.3	2.0	3.1
1989	2.8	2.4	2.0	3.1
1990	2.8	2.4	2.0	3.2
1991	2.9	2.4	2.1	3.3
1992	2.9	2.5	2.1	3.4
1993	3.0	2.5	2.1	3.5
1994	3.0	2.5	2.2	3.5
1995	3.1	2.6	2.2	3.6
1996	3.2	2.6	2.2	3.7
1997	3.2	2.7	2.3	3.8
1998	3.3	2.7	2.3	3.9
1999	3.4	2.8	2.4	4.0
2000	3.4	2.8	2.4	4.1
2001	3.5	2.8	2.4	4.2
2002	3.6	2.9	2.5	4.3
2003	3.6	2.9	2.5	4.4
2004	3.7	3.0	2.6	4.6
2005	3.8	3.0	2.6	4.7
APC0	**2.02***	**1.58***	**1.67***	**1.85***
APC1	–	–	–	-2.61
APC2	–	–	–	**2.55***

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.13(a): GALLBLADDER (ICD-10 : C23-C24) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

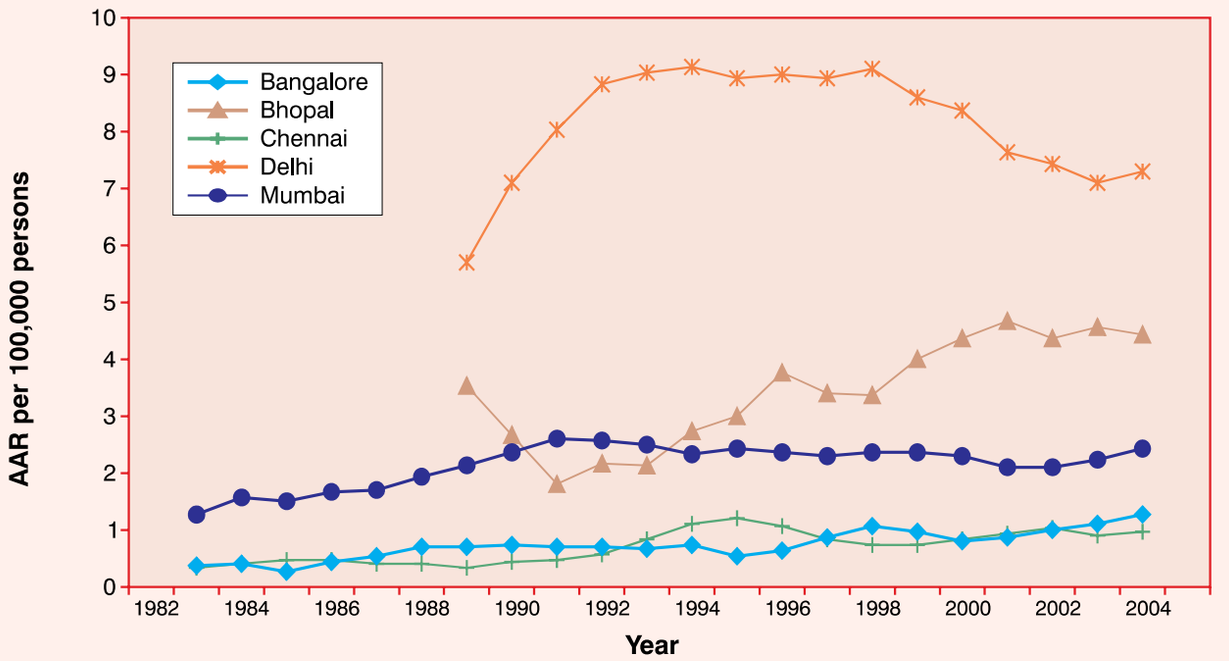


Table 4.13(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	0.0		0.2		0.9
1983	0.6		0.3		1.6
1984	0.3		0.5		1.3
1985	0.3		0.4		1.8
1986	0.2		0.5		1.4
1987	0.8		0.5		1.8
1988	0.6	4.1	0.2	4.2	1.9
1989	0.7	4.8	0.5	6.2	2.1
1990	0.8	1.7	0.3	6.7	2.4
1991	0.7	1.5	0.5	8.4	2.6
1992	0.6	2.2	0.6	9.0	2.8
1993	0.8	2.8	0.6	9.1	2.3
1994	0.6	1.4	1.3	9.0	2.4
1995	0.8	4.0	1.4	9.3	2.3
1996	0.2	3.6	0.9	8.5	2.6
1997	0.9	3.7	0.9	9.2	2.2
1998	1.5	2.9	0.7	9.1	2.1
1999	0.8	3.5	0.6	9.0	2.8
2000	0.6	5.6	0.9	7.7	2.2
2001	1.0	4.0	1.0	8.4	1.9
2002	1.0	4.4	0.9	6.8	2.2
2003	1.0	4.7	1.2	7.1	2.2
2004	1.3	4.6	0.6	7.4	2.3
2005	1.5	4.0	1.1	7.4	2.8
Slope(b)	**0.040**	**0.114**	**0.034**	**0.045**	**0.044**
p-value	**0.001**	**0.033**	**0.001**	0.477	**0.001**

Fig. 4.13(b): GALLBLADDER (ICD-10 : C23-C24) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

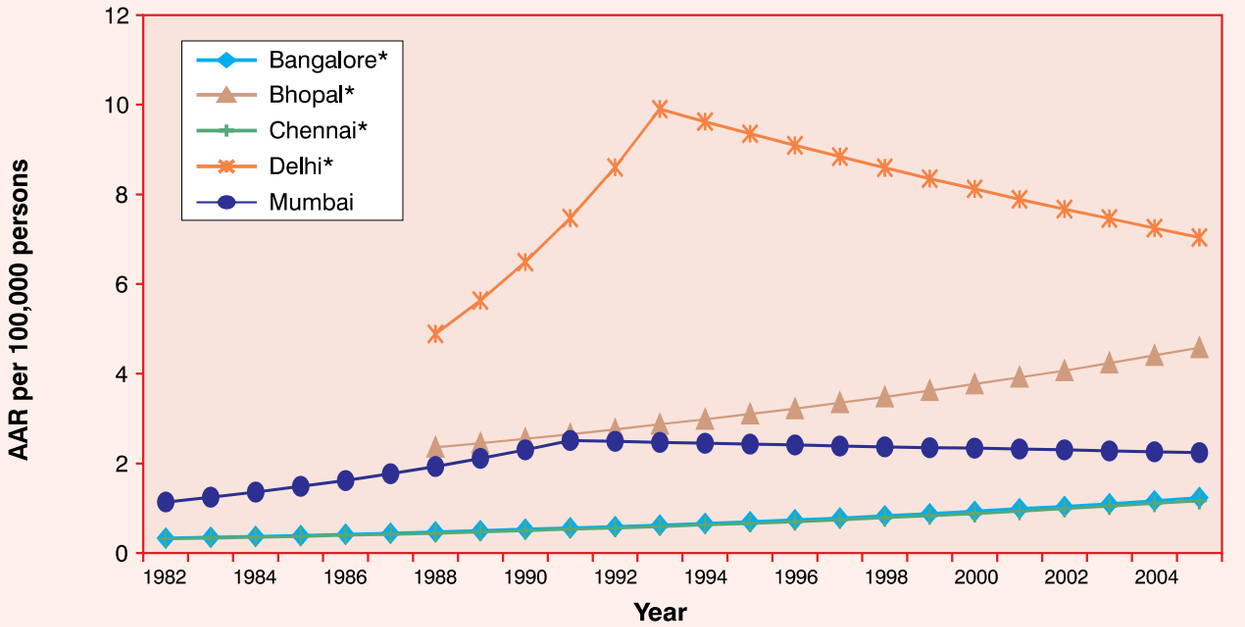


Table 4.13(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore[$]	Bhopal	Chennai[$]	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP1*	JP1*
1982	0.3		0.3		1.1
1983	0.4		0.3		1.3
1984	0.4		0.4		1.4
1985	0.4		0.4		1.5
1986	0.4		0.4		1.6
1987	0.4		0.4		1.8
1988	0.5	2.4	0.4	4.9	1.9
1989	0.5	2.5	0.5	5.6	2.1
1990	0.5	2.6	0.5	6.5	2.3
1991	0.6	2.7	0.5	7.5	**2.5**
1992	0.6	2.8	0.6	8.6	2.5
1993	0.6	2.9	0.6	**9.9**	2.5
1994	0.7	3.0	0.6	9.6	2.5
1995	0.7	3.1	0.7	9.4	2.4
1996	0.7	3.2	0.7	9.1	2.4
1997	0.8	3.4	0.7	8.8	2.4
1998	0.8	3.5	0.8	8.6	2.4
1999	0.9	3.6	0.8	8.4	2.4
2000	0.9	3.8	0.9	8.1	2.3
2001	1.0	3.9	0.9	7.9	2.3
2002	1.0	4.1	1.0	7.7	2.3
2003	1.1	4.2	1.1	7.5	2.3
2004	1.2	4.4	1.1	7.3	2.3
2005	1.2	4.6	1.2	7.0	2.2
APC0	**5.88***	**3.99***	**5.87***	0.93	**2.53***
APC1	–	–	–	**15.13***	**9.14***
APC2	–	–	–	**-2.79***	-0.8

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*
[$] Kindly note the trend values in the 2 PBCRs are identical and therefore only one line is visible in the graph.

Fig. 4.14(a): LARYNX (ICD-10 : C32) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

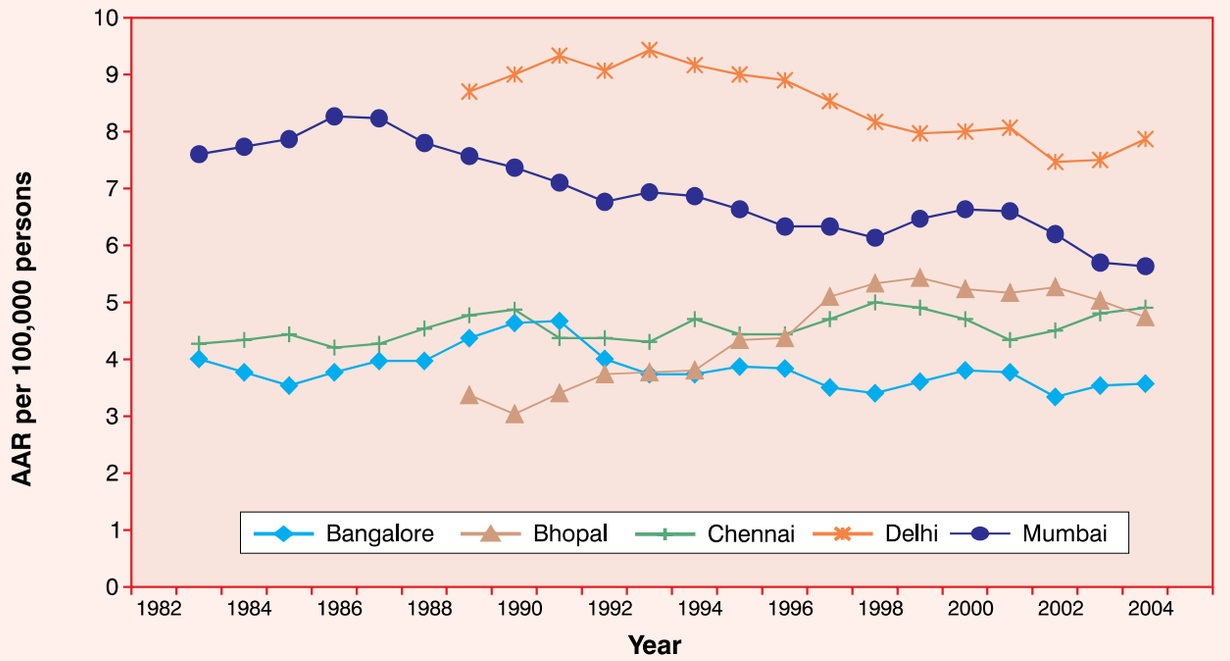


Table 4.14(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	4.0		4.2		6.7
1983	4.4		3.7		8.5
1984	3.6		4.9		7.6
1985	3.3		4.4		7.1
1986	3.7		4.0		8.9
1987	4.3		4.2		8.8
1988	3.9	5.1	4.6	7.4	7.0
1989	3.7	2.6	4.8	8.3	7.6
1990	5.5	2.4	4.9	10.4	8.1
1991	4.7	4.1	4.9	8.3	6.4
1992	3.8	3.7	3.3	9.3	6.8
1993	3.5	3.4	4.9	9.6	7.1
1994	3.9	4.2	4.7	9.4	6.9
1995	3.8	3.8	4.5	8.5	6.6
1996	3.9	5.0	4.1	9.1	6.4
1997	3.8	4.3	4.7	9.1	6.0
1998	2.8	6.0	5.3	7.4	6.6
1999	3.6	5.7	5.0	8.0	5.8
2000	4.4	4.6	4.4	8.5	7.0
2001	3.4	5.4	4.7	7.5	7.1
2002	3.5	5.5	3.9	8.2	5.7
2003	3.1	4.9	4.9	6.7	5.8
2004	4.0	4.7	5.6	7.6	5.6
2005	3.6	4.6	4.2	9.3	5.5
Slope(b)	**-0.024**	**0.111**	**0.024**	**-0.062**	**-0.102**
p-value	0.140	**0.010**	0.118	0.160	**0.001**

Fig. 4.14(b): LARYNX (ICD-10 : C32) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

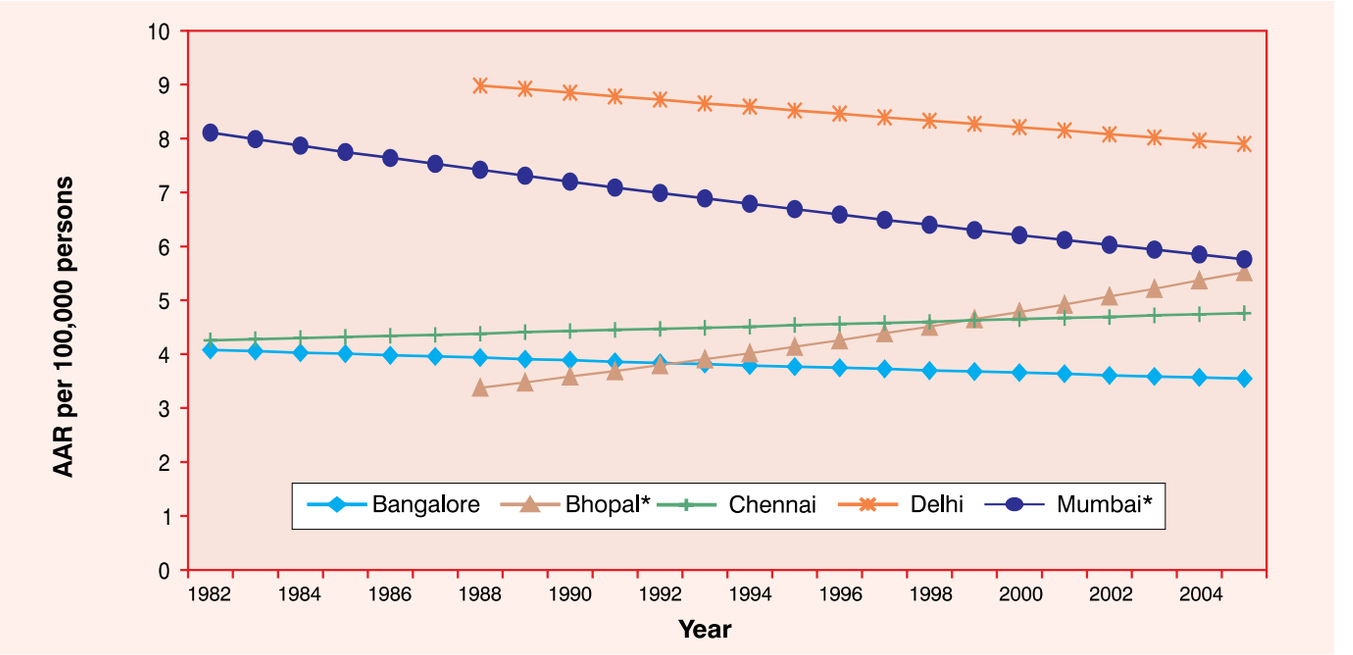


Table 4.14(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*	JP0*
1982	4.1		4.3		8.1
1983	4.1		4.3		8.0
1984	4.0		4.3		7.9
1985	4.0		4.3		7.8
1986	4.0		4.3		7.6
1987	4.0		4.4		7.5
1988	3.9	3.4	4.4	9.0	7.4
1989	3.9	3.5	4.4	8.9	7.3
1990	3.9	3.6	4.4	8.9	7.2
1991	3.9	3.7	4.5	8.8	7.1
1992	3.8	3.8	4.5	8.7	7.0
1993	3.8	3.9	4.5	8.7	6.9
1994	3.8	4.0	4.5	8.6	6.8
1995	3.8	4.1	4.5	8.5	6.7
1996	3.8	4.3	4.6	8.5	6.6
1997	3.7	4.4	4.6	8.4	6.5
1998	3.7	4.5	4.6	8.3	6.4
1999	3.7	4.7	4.6	8.3	6.3
2000	3.7	4.8	4.7	8.2	6.2
2001	3.6	4.9	4.7	8.2	6.1
2002	3.6	5.1	4.7	8.1	6.0
2003	3.6	5.2	4.7	8.0	5.9
2004	3.6	5.4	4.7	8.0	5.9
2005	3.6	5.5	4.8	7.9	5.8
APC0	-0.61	**2.92***	0.49	-0.75	**-1.47***
APC1	–	–	–	–	–
APC2	–	–	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.15(a): LUNG (ICD-10 : C33-C34) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

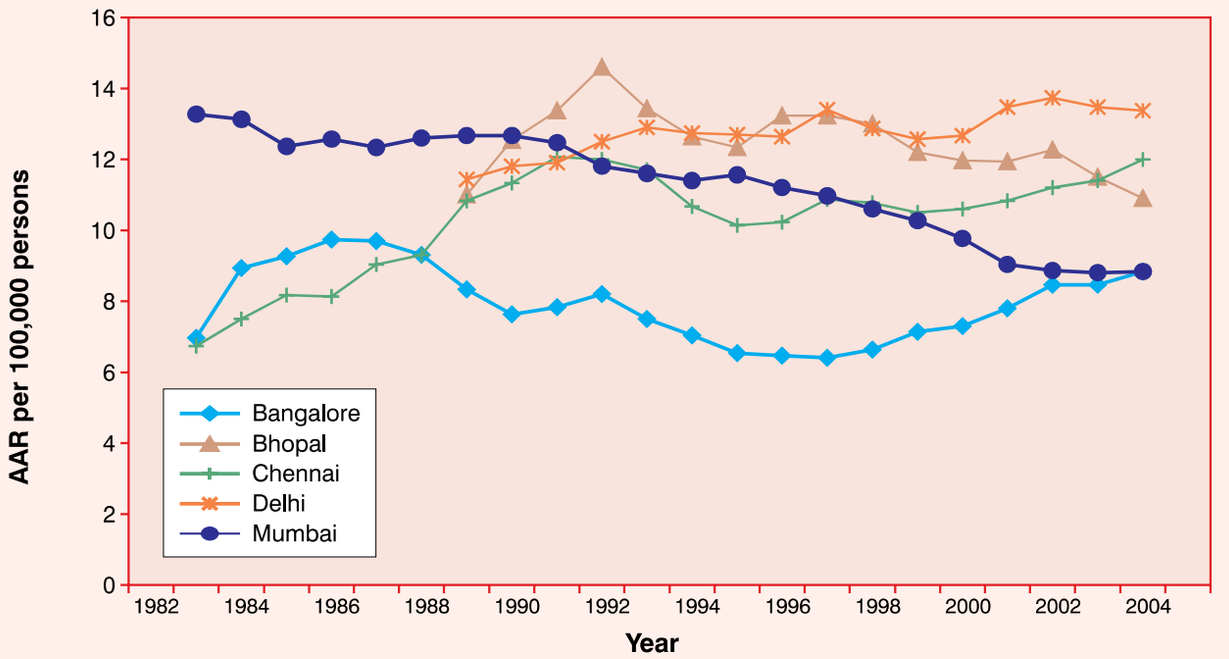


Table 4.15(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	4.7		5.0		13.3
1983	7.9		7.1		14.0
1984	8.3		8.1		12.5
1985	10.6		7.3		12.9
1986	8.9		9.1		11.7
1987	9.7		8.0		13.1
1988	10.5	10.1	10.0	10.5	12.2
1989	7.7	12.5	9.9	11.3	12.5
1990	6.8	10.4	12.6	12.0	13.3
1991	8.4	14.7	11.5	12.1	12.2
1992	8.3	15.0	12.1	11.6	11.9
1993	7.9	14.1	12.4	13.8	11.3
1994	6.3	11.2	10.6	13.3	11.6
1995	6.9	12.6	9.0	11.1	11.3
1996	6.4	13.2	10.8	13.7	11.8
1997	6.1	13.9	10.9	13.1	10.5
1998	6.7	12.6	10.9	13.4	10.6
1999	7.1	12.5	10.5	12.1	10.7
2000	7.6	11.5	10.1	12.2	9.5
2001	7.2	11.9	11.2	13.7	9.1
2002	8.6	12.4	11.2	14.5	8.5
2003	9.6	12.5	11.2	13.0	9.0
2004	7.2	9.6	11.8	12.9	8.9
2005	9.7	10.6	13.0	14.2	8.6
Slope(b)	**-0.013**	**-0.075**	**0.198**	**0.139**	**-0.217**
p-value	0.776	0.306	**0.001**	**0.004**	**0.001**

Fig. 4.15(b): LUNG (ICD-10 : C33-C34) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

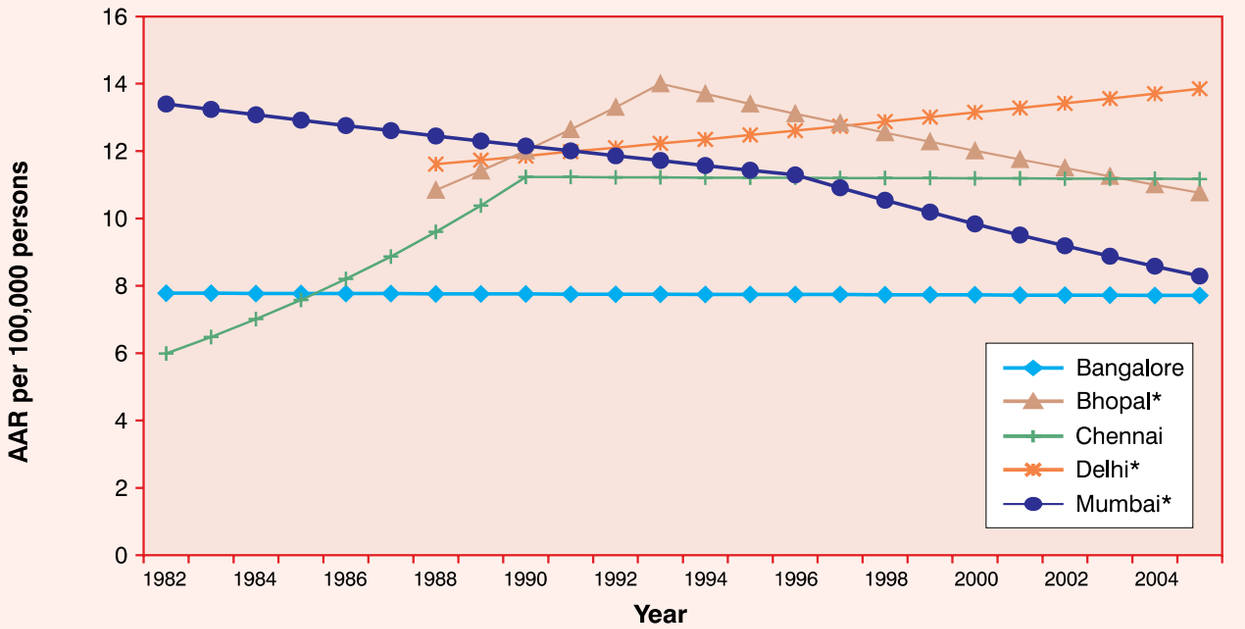


Table 4.15(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	**JP1***	**JP1***	**JP0***	**JP1***
1982	7.8		6.0		13.4
1983	7.8		6.5		13.2
1984	7.8		7.0		13.1
1985	7.8		7.6		12.9
1986	7.8		8.2		12.8
1987	7.8		8.9		12.6
1988	7.8	10.8	9.6	11.6	12.5
1989	7.8	11.4	10.4	11.7	12.3
1990	7.8	12.0	**11.2**	11.9	12.2
1991	7.8	12.6	11.2	12.0	12.0
1992	7.8	13.3	11.2	12.1	11.9
1993	7.8	**14.0**	11.2	12.2	11.7
1994	7.7	13.7	11.2	12.4	11.6
1995	7.7	13.4	11.2	12.5	11.4
1996	7.7	13.1	11.2	12.6	**11.3**
1997	7.7	12.8	11.2	12.7	10.9
1998	7.7	12.6	11.2	12.9	10.5
1999	7.7	12.3	11.2	13.0	10.2
2000	7.7	12.0	11.2	13.2	9.8
2001	7.7	11.8	11.2	13.3	9.5
2002	7.7	11.5	11.2	13.4	9.2
2003	7.7	11.3	11.2	13.6	8.9
2004	7.7	11.0	11.2	13.7	8.6
2005	7.7	10.8	11.2	13.9	8.3
APC0	-0.04	-0.57	**2.25***	**1.04***	**-1.97***
APC1	–	5.25	**8.16***	–	**-1.22***
APC2	–	**-2.17***	-0.03	–	**-3.38***

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.16(a): LUNG (ICD-10 : C33-C34) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

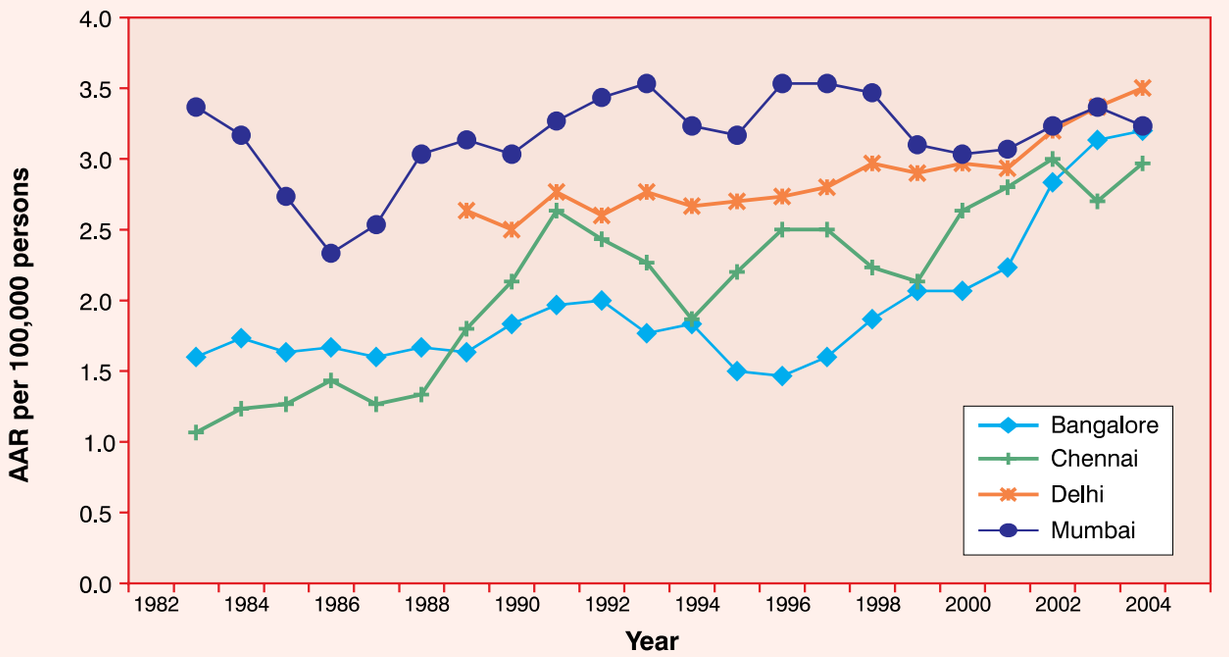


Table 4.16(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	1.2	1.1		3.2
1983	1.6	1.3		3.1
1984	2.0	0.8		3.8
1985	1.6	1.6		2.6
1986	1.3	1.4		1.8
1987	2.1	1.3		2.6
1988	1.4	1.1	2.6	3.2
1989	1.5	1.6	2.1	3.3
1990	2.0	2.7	3.2	2.9
1991	2.0	2.1	2.2	2.9
1992	1.9	3.1	2.9	4.0
1993	2.1	2.1	2.7	3.4
1994	1.3	1.6	2.7	3.2
1995	2.1	1.9	2.6	3.1
1996	1.1	3.1	2.8	3.2
1997	1.2	2.5	2.8	4.3
1998	2.5	1.9	2.8	3.1
1999	1.9	2.3	3.3	3.0
2000	1.8	2.2	2.6	3.2
2001	2.5	3.4	3.0	2.9
2002	2.4	2.8	3.2	3.1
2003	3.6	2.8	3.4	3.7
2004	3.4	2.5	3.5	3.3
2005	2.6	3.6	3.6	2.7
Slope(b)	**0.057**	**0.087**	**0.056**	**0.012**
p-value	**0.023**	**0.001**	**0.001**	0.421

Fig. 4.16(b): LUNG (ICD-10 : C33-C34) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

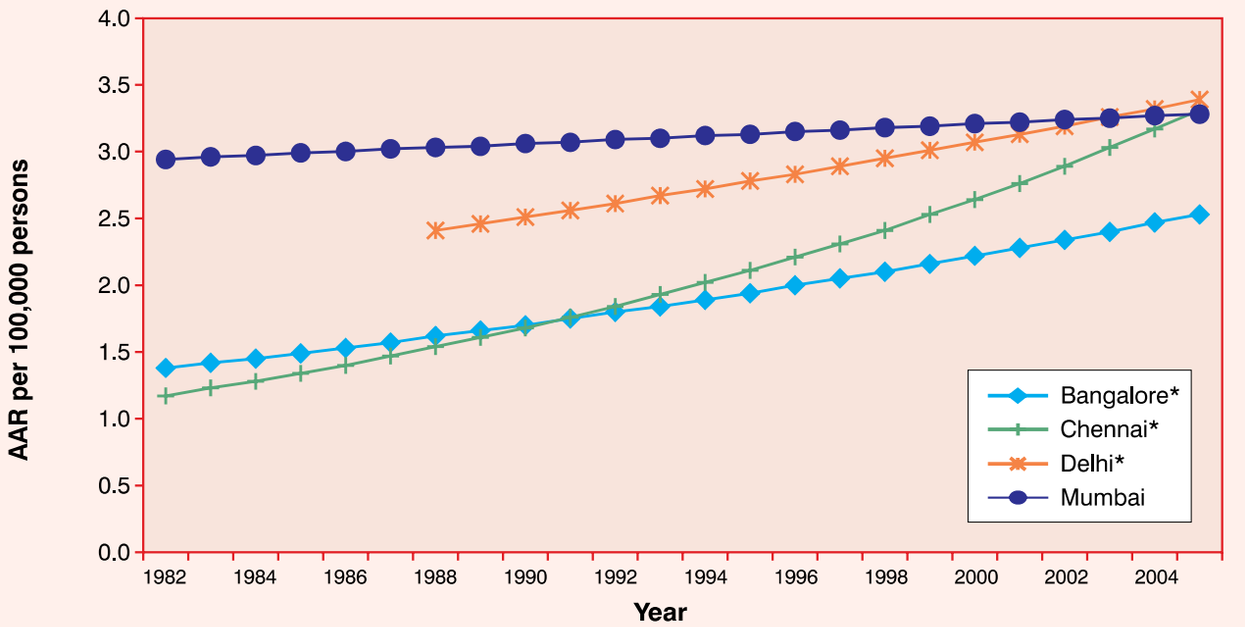


Table 4.16(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*
1982	1.4	1.2		2.9
1983	1.4	1.2		3.0
1984	1.5	1.3		3.0
1985	1.5	1.3		3.0
1986	1.5	1.4		3.1
1987	1.6	1.5		3.0
1988	1.6	1.5	2.4	3.0
1989	1.7	1.6	2.5	3.0
1990	1.7	1.7	2.5	3.1
1991	1.8	1.8	2.6	3.1
1992	1.8	1.8	2.6	3.1
1993	1.8	1.9	2.7	3.1
1994	1.9	2.0	2.7	3.1
1995	1.9	2.1	2.8	3.1
1996	2.0	2.2	2.8	3.2
1997	2.1	2.3	2.9	3.2
1998	2.1	2.4	3.0	3.2
1999	2.2	2.5	3.0	3.2
2000	2.2	2.6	3.1	3.2
2001	2.3	2.8	3.1	3.2
2002	2.3	2.9	3.2	3.2
2003	2.4	3.0	3.3	3.3
2004	2.5	3.2	3.3	3.3
2005	2.5	3.3	3.4	3.3
APC0	2.67*	4.62*	2.02*	0.47
APC1	–	–	–	–
APC2	–	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.17(a): BREAST (ICD-10 : C50) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

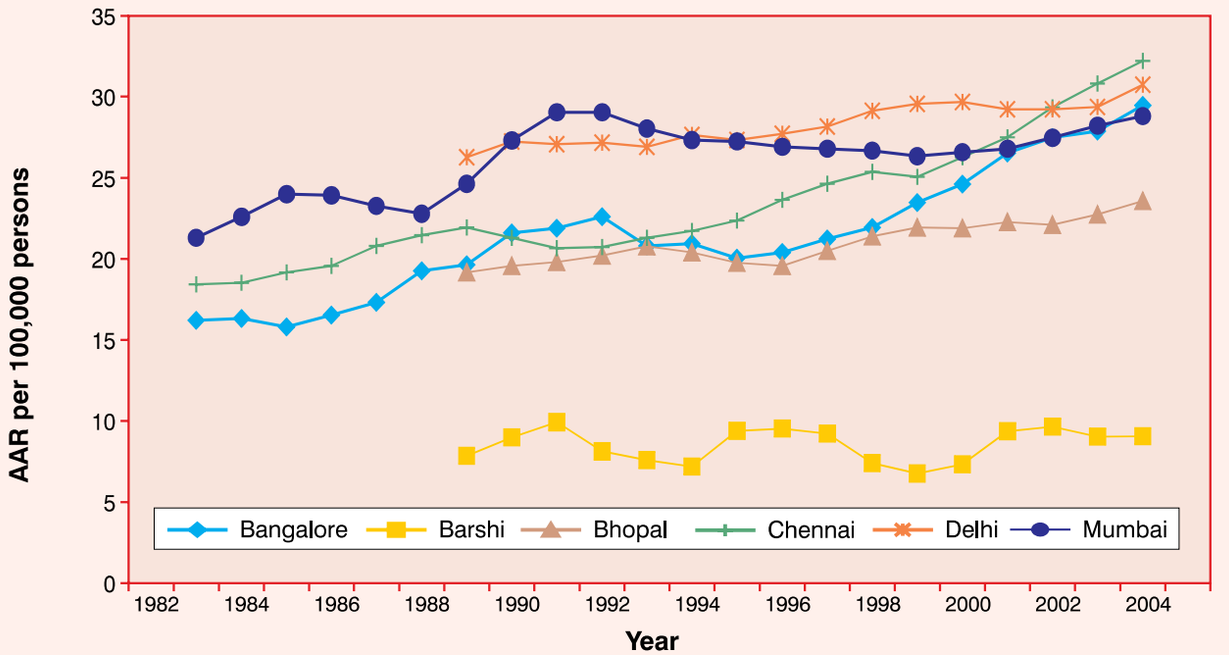


Table 4.17(a): Year wise AARs

Year	Bangalore	Barshi	Bhopal	Chennai	Delhi	Mumbai
1982	15.8			18.4		20.8
1983	16.0			18.2		20.7
1984	16.8			18.7		22.4
1985	16.2			18.7		24.7
1986	14.4			20.1		24.9
1987	19.0			19.9		22.2
1988	18.6	7.2	18.2	22.4	24.8	22.7
1989	20.2	6.6	19.5	22.1	26.9	23.5
1990	20.1	9.8	19.8	21.3	27.1	27.7
1991	24.5	10.6	19.4	20.5	27.7	30.7
1992	21.1	9.4	20.2	20.2	26.4	28.7
1993	22.2	4.4	21.0	21.5	27.4	27.7
1994	19.1	9.0	21.1	22.2	26.9	27.7
1995	21.5	8.2	19.1	21.5	28.6	26.6
1996	19.5	11.0	19.1	23.4	26.5	27.4
1997	20.2	9.4	20.5	26.0	28.0	26.7
1998	24.0	7.3	21.9	24.5	30.0	26.3
1999	21.6	5.5	21.8	25.6	29.4	27.0
2000	24.8	7.5	22.1	25.1	29.3	25.7
2001	27.4	9.0	21.8	28.1	30.3	27.0
2002	27.4	11.6	22.9	29.3	28.1	27.7
2003	27.6	8.4	21.6	30.6	29.3	27.7
2004	28.6	7.1	23.7	32.5	30.7	29.2
2005	32.2	11.7	25.4	33.5	32.2	29.5
Slope(b)	**0.587**	**0.074**	**0.293**	**0.587**	**0.292**	**0.283**
p-value	**0.001**	0.438	**0.001**	**0.001**	**0.001**	**0.001**

Fig. 4.17(b): BREAST (ICD-10 : C50) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

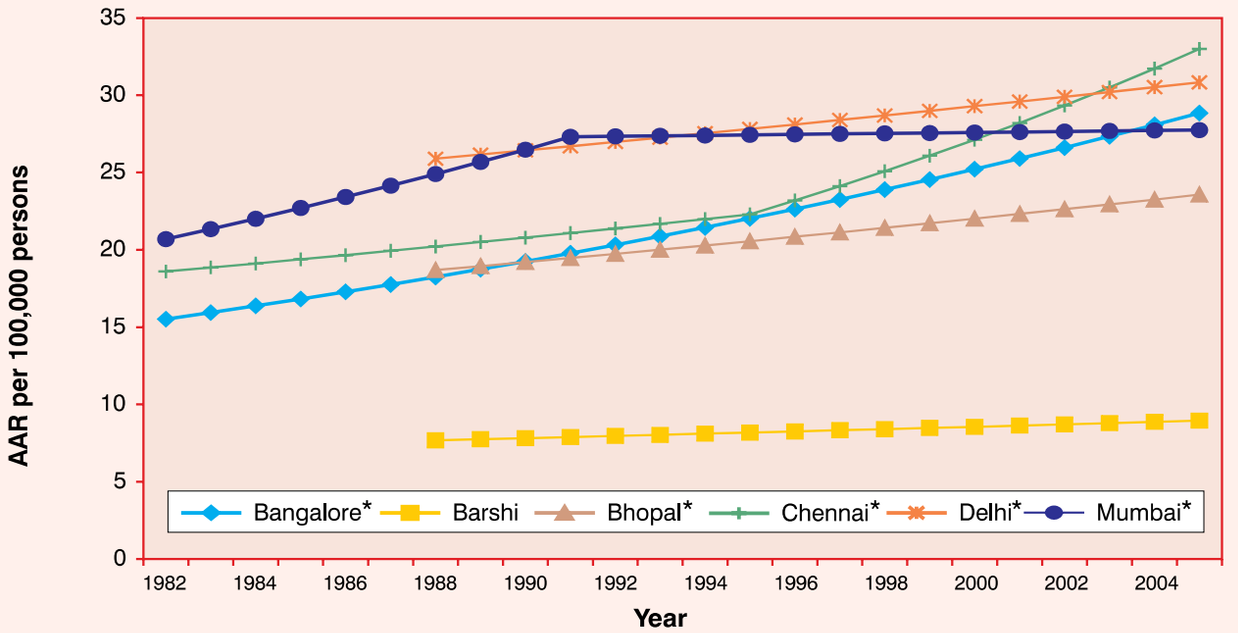


Table 4.17(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Barshi	Bhopal	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP1*	JP0*	JP1*
1982	15.5			18.6		20.7
1983	15.9			18.9		21.3
1984	16.4			19.1		22.0
1985	16.8			19.4		22.7
1986	17.3			19.7		23.4
1987	17.8			19.9		24.1
1988	18.2	7.7	18.7	20.2	26.0	24.9
1989	18.7	7.8	19.0	20.5	26.2	25.7
1990	19.3	7.8	19.2	20.8	26.4	26.5
1991	19.8	7.9	19.5	21.1	26.7	**27.3**
1992	20.3	8.0	19.7	21.4	27.0	27.3
1993	20.9	8.0	20.0	21.7	27.3	27.4
1994	21.4	8.1	20.3	22.0	27.5	27.4
1995	22.0	8.2	20.6	**22.3**	27.8	27.4
1996	22.6	8.3	20.9	23.2	28.1	27.5
1997	23.3	8.3	21.1	24.1	28.4	27.5
1998	23.9	8.4	21.4	25.1	28.7	27.5
1999	24.5	8.5	21.7	26.1	29.0	27.6
2000	25.2	8.6	22.0	27.1	29.3	27.6
2001	25.9	8.6	22.3	28.2	29.6	27.6
2002	26.6	8.7	22.6	29.3	29.9	27.7
2003	27.3	8.8	22.9	30.5	30.2	27.7
2004	28.1	8.9	23.3	31.7	30.5	27.7
2005	28.9	9.0	23.6	33.0	30.8	27.8
APC0	2.73*	0.9	1.38*	2.45*	1.03*	1.15*
APC1	–	–	–	1.40*	–	3.13*
APC2	–	–	–	4.00*	–	0.11

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.18(a): CERVIX (ICD-10 : C53) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

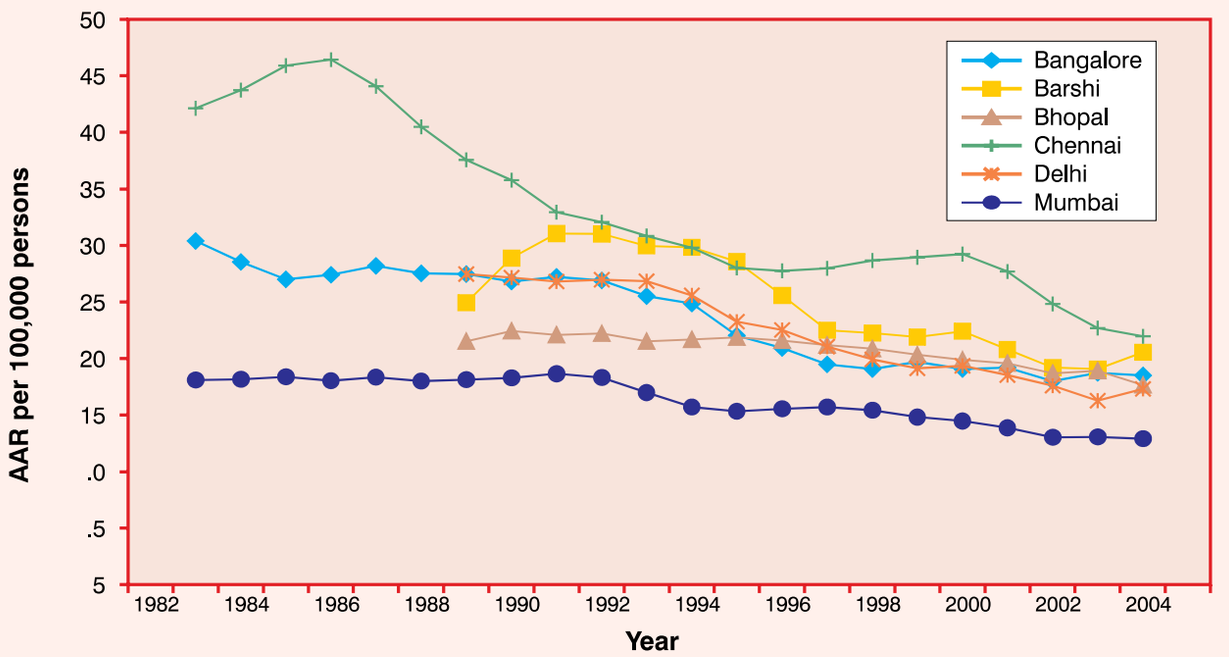


Table 4.18(a): Year wise AARs

Year	Bangalore	Barshi	Bhopal	Chennai	Delhi	Mumbai
1982	32.4			41.0		17.9
1983	30.6			43.5		17.8
1984	28.2			41.9		18.6
1985	26.8			45.8		18.1
1986	26.0			50.0		18.4
1987	29.4			43.5		17.6
1988	29.2	22.1	21.7	38.8	25.9	19.0
1989	24.0	24.9	21.8	39.2	28.4	17.4
1990	29.2	27.8	21.1	34.7	28.1	18.0
1991	27.2	34.0	24.4	33.4	25.0	19.4
1992	25.3	31.4	20.8	30.7	27.3	18.6
1993	28.2	27.7	21.4	32.1	28.6	16.9
1994	23.1	30.8	22.4	29.7	24.6	15.5
1995	23.3	31.0	21.2	27.6	23.5	14.7
1996	19.7	23.9	22.0	26.7	21.7	15.8
1997	19.8	21.8	21.6	29.0	22.4	16.1
1998	18.9	21.8	19.9	28.2	19.1	15.2
1999	18.5	23.1	21.1	28.8	18.3	15.0
2000	21.7	20.8	20.0	29.8	20.0	14.3
2001	17.0	23.3	18.6	29.1	19.8	14.1
2002	18.9	18.3	20.1	24.2	15.8	13.2
2003	18.1	16.0	17.4	21.2	17.2	11.8
2004	19.2	22.9	19.2	22.7	15.8	14.2
2005	18.2	22.7	16.4	22.0	18.9	12.7
Slope	**-0.611**	**-0.554**	**-0.271**	**-1.051**	**-0.747**	**-0.271**
p-value	**0.001**	**0.007**	**0.001**	**0.001**	**0.001**	**0.001**

Fig. 4.18(b): CERVIX (ICD-10 : C53) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

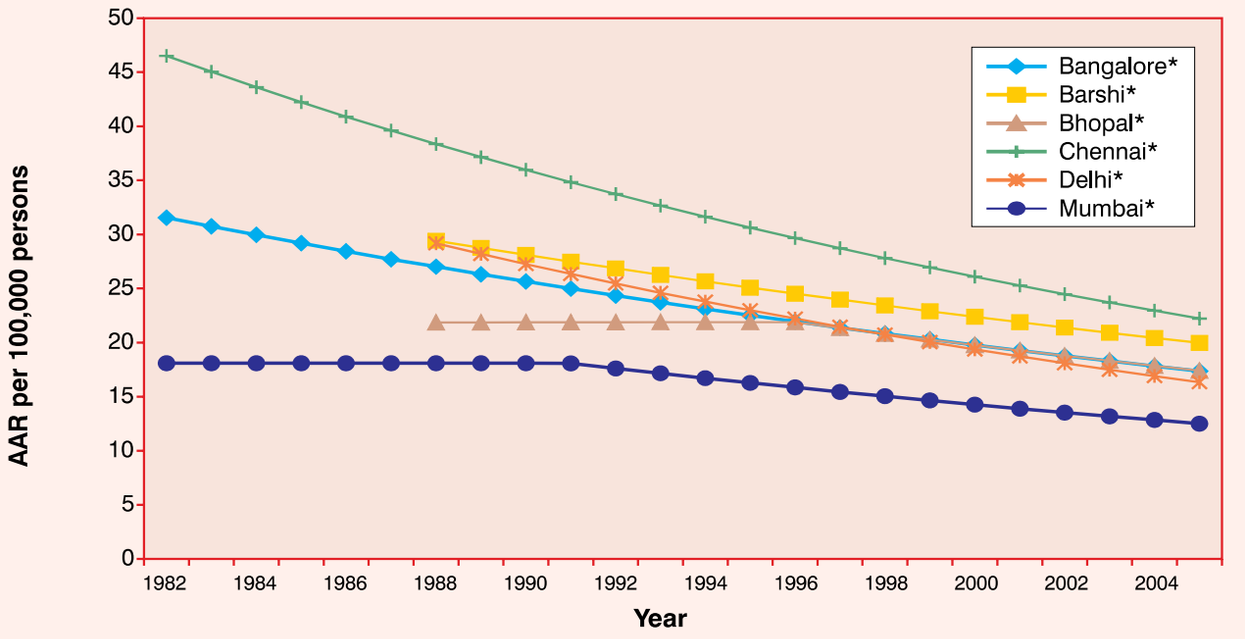


Table 4.18(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Barshi	Bhopal	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP1*	JP0*	JP0*	JP1*
1982	31.6			46.5		18.1
1983	30.8			45.0		18.1
1984	30.0			43.6		18.1
1985	29.2			42.2		18.1
1986	28.4			40.9		18.1
1987	27.7			39.6		18.1
1988	27.0	29.4	21.9	38.4	29.2	18.1
1989	26.3	28.8	21.9	37.1	28.2	18.1
1990	25.6	28.1	21.9	36.0	27.3	18.1
1991	25.0	27.5	21.9	34.8	26.3	**18.1**
1992	24.3	26.9	21.9	33.7	25.5	17.6
1993	23.7	26.3	21.9	32.7	24.6	17.2
1994	23.1	25.7	21.9	31.6	23.8	16.7
1995	22.5	25.1	**21.9**	30.6	23.0	16.3
1996	21.9	24.5	21.9	29.7	22.2	15.9
1997	21.4	24.0	21.3	28.7	21.5	15.4
1998	20.8	23.4	20.8	27.8	20.8	15.0
1999	20.3	22.9	20.3	26.9	20.1	14.7
2000	19.8	22.4	19.8	26.1	19.4	14.3
2001	19.3	21.9	19.3	25.3	18.7	13.9
2002	18.8	21.4	18.8	24.5	18.1	13.5
2003	18.3	20.9	18.3	23.7	17.5	13.2
2004	17.8	20.4	17.9	23.0	16.9	12.8
2005	17.4	20.0	17.4	22.2	16.3	12.5
APC0	-2.56*	-2.25*	-1.36*	-3.16*	-3.35*	-1.71*
APC1	–	–	0.02	–	–	-0.01
APC2	–	–	-2.51*	–	–	-2.60*

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.19(a): CORPUS UTERI (ICD-10 : C54) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

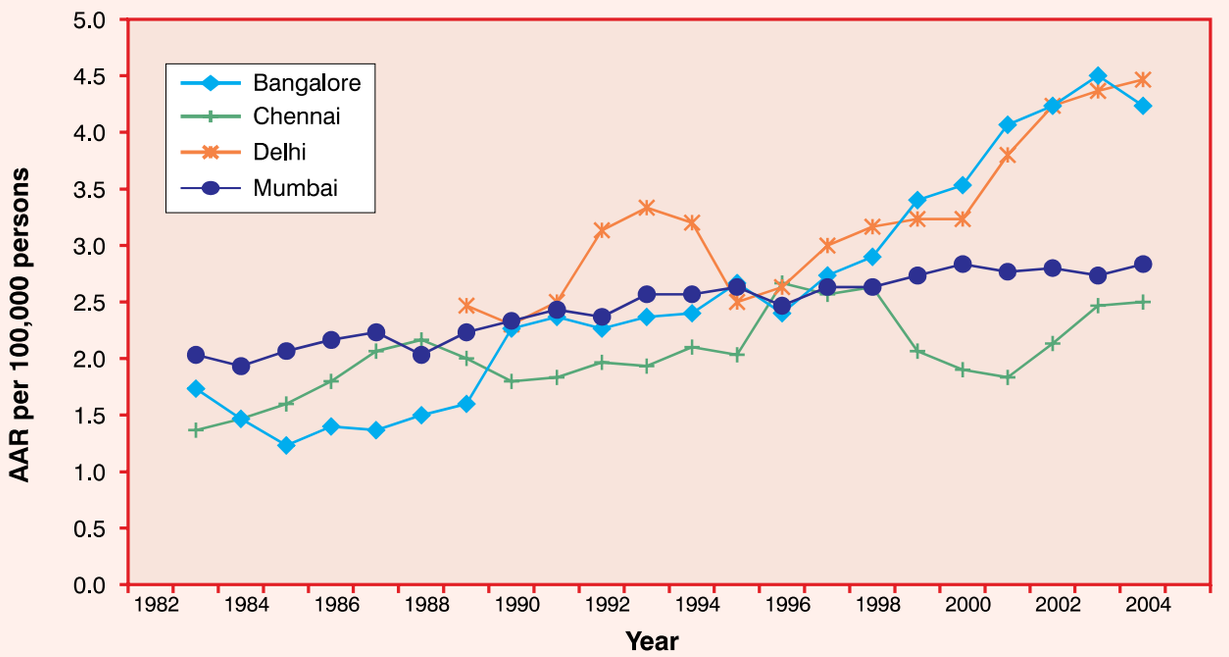


Table 4.19(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	1.7	1.3		2.1
1983	2.1	1.0		2.1
1984	1.4	1.8		1.9
1985	0.9	1.6		1.8
1986	1.4	1.4		2.5
1987	1.9	2.4		2.2
1988	0.8	2.4	2.6	2.0
1989	1.8	1.7	2.4	1.9
1990	2.2	1.9	2.4	2.8
1991	2.8	1.8	2.1	2.3
1992	2.1	1.8	3.0	2.2
1993	1.9	2.3	4.3	2.6
1994	3.1	1.7	2.7	2.9
1995	2.2	2.3	2.6	2.2
1996	2.7	2.1	2.2	2.8
1997	2.3	3.6	3.1	2.4
1998	3.2	2.0	3.7	2.7
1999	3.2	2.3	2.7	2.8
2000	3.8	1.9	3.3	2.7
2001	3.6	1.5	3.7	3.0
2002	4.8	2.1	4.4	2.6
2003	4.3	2.8	4.6	2.8
2004	4.4	2.5	4.1	2.8
2005	4.0	2.2	4.7	2.9
Slope	**0.140**	**0.039**	**0.124**	**0.041**
p-value	**0.001**	**0.010**	**0.001**	**0.001**

Fig. 4.19(b): CORPUS UTERI (ICD-10 : C54) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

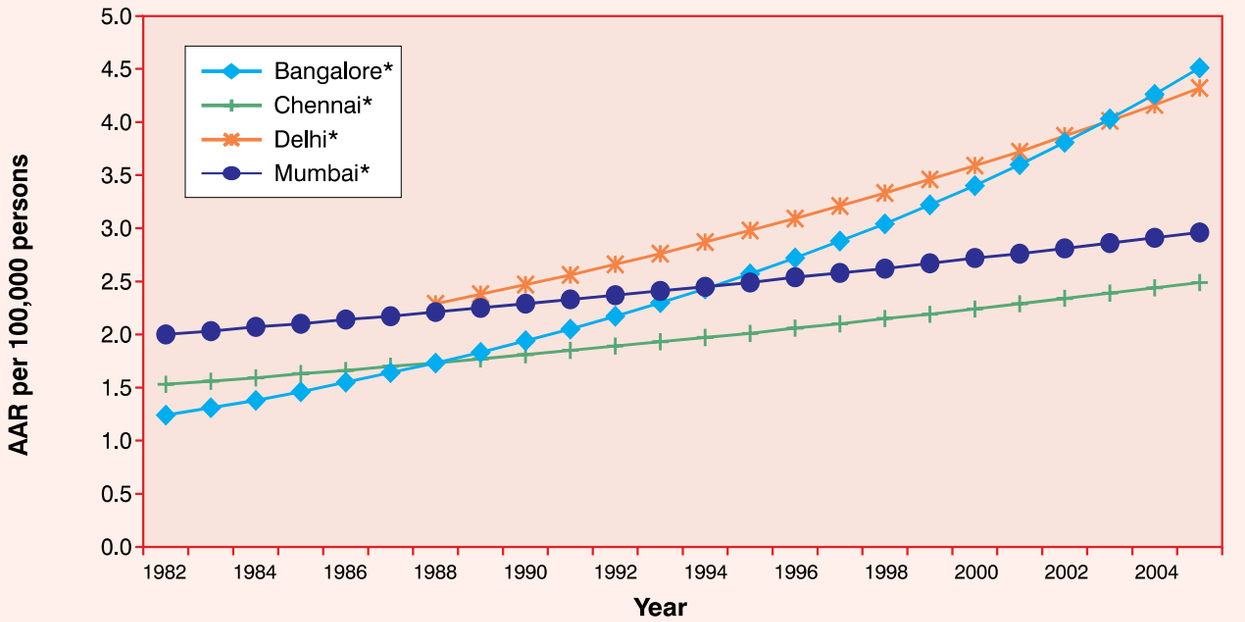


Table 4.19(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*
1982	1.2	1.5		2
1983	1.3	1.6		2.0
1984	1.4	1.6		2.1
1985	1.5	1.6		2.1
1986	1.6	1.7		2.1
1987	1.6	1.7		2.2
1988	1.7	1.7	2.3	2.2
1989	1.8	1.8	2.4	2.3
1990	1.9	1.8	2.5	2.3
1991	2.1	1.9	2.6	2.3
1992	2.2	1.9	2.7	2.4
1993	2.3	1.9	2.8	2.4
1994	2.4	2.0	2.9	2.5
1995	2.6	2.0	3.0	2.5
1996	2.7	2.1	3.1	2.5
1997	2.9	2.1	3.2	2.6
1998	3.0	2.2	3.3	2.6
1999	3.2	2.2	3.5	2.7
2000	3.4	2.2	3.6	2.7
2001	3.6	2.3	3.7	2.8
2002	3.8	2.3	3.9	2.8
2003	4.0	2.4	4.0	2.9
2004	4.3	2.4	4.2	2.9
2005	4.5	2.5	4.3	3.0
APC0	5.79*	2.15*	3.80*	1.73*
APC1	–	–	–	–
APC2	–	–	–	–

Values of years where a shift in trend observed is highlighted; represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.20(a): OVARY (ICD-10 : C56) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

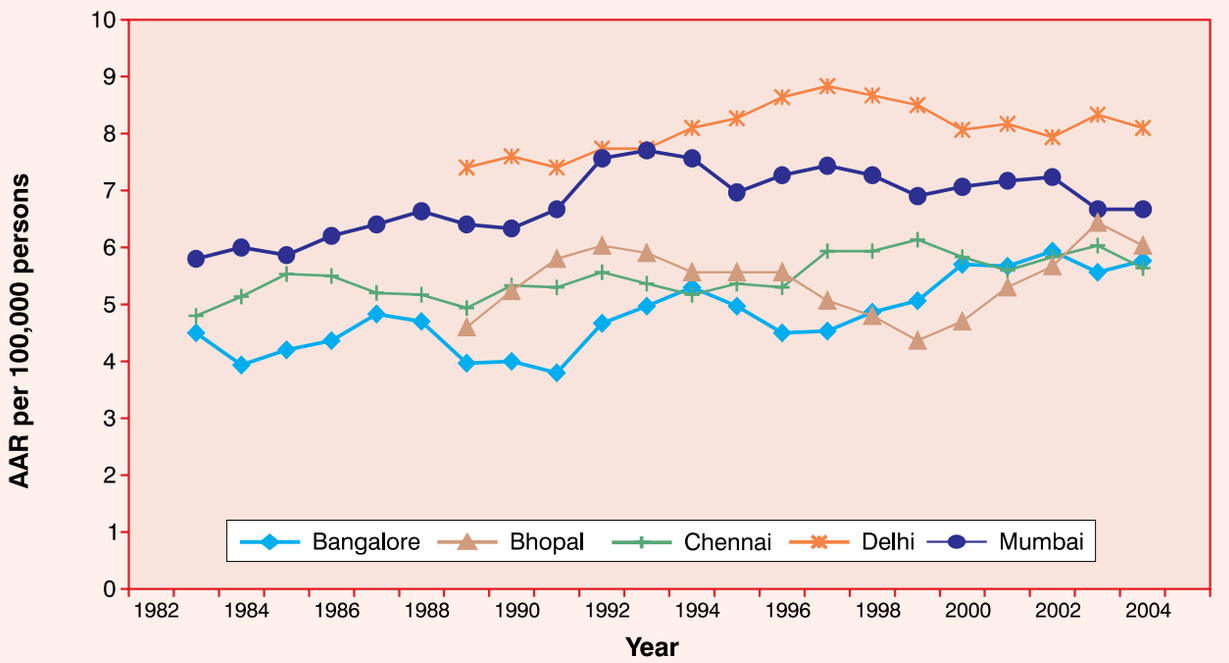


Table 4.20(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	4.6		4.2		5.6
1983	3.9		4.4		6
1984	5.0		5.8		5.8
1985	2.9		5.2		6.2
1986	4.7		5.6		5.6
1987	5.5		5.7		6.8
1988	4.3	3.7	4.3	7.3	6.8
1989	4.3	5.5	5.5	8.0	6.3
1990	3.3	4.6	5.0	6.9	6.1
1991	4.4	5.6	5.5	7.9	6.6
1992	3.7	7.2	5.4	7.4	7.3
1993	5.9	5.3	5.8	7.9	8.8
1994	5.3	5.2	4.9	7.9	7.0
1995	4.7	6.2	4.8	8.5	6.9
1996	4.9	5.3	6.4	8.4	7.0
1997	3.9	5.2	4.7	9.0	7.9
1998	4.8	4.7	6.7	9.1	7.4
1999	5.9	4.5	6.4	7.9	6.5
2000	4.5	3.9	5.3	8.5	6.8
2001	6.7	5.7	5.8	7.8	7.9
2002	5.8	6.3	5.7	8.2	6.8
2003	5.3	5.0	6.0	7.8	7.0
2004	5.6	8.0	6.4	9.0	6.2
2005	6.4	5.1	4.5	7.5	6.8
Slope	**0.079**	**0.044**	**0.040**	**0.046**	**0.051**
p-value	**0.003**	0.378	**0.049**	0.095	**0.019**

Fig. 4.20(b): OVARY (ICD-10 : C56) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

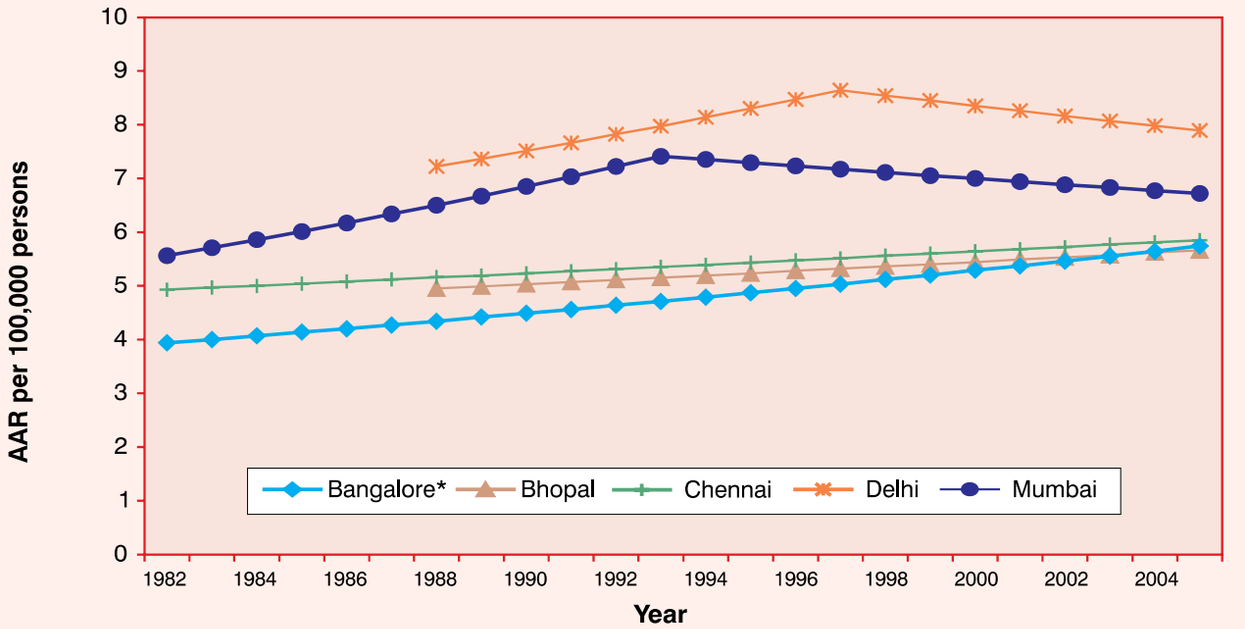


Table 4.20(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP1*	JP1*
1982	3.9		4.9		5.6
1983	4.0		5.0		5.7
1984	4.1		5.0		5.9
1985	4.1		5.0		6.0
1986	4.2		5.1		6.2
1987	4.3		5.1		6.3
1988	4.3	5.0	5.2	7.2	6.5
1989	4.4	5.0	5.2	7.4	6.7
1990	4.5	5.0	5.2	7.5	6.9
1991	4.6	5.1	5.3	7.7	7.0
1992	4.6	5.1	5.3	7.8	7.2
1993	4.7	5.2	5.4	8.0	7.4
1994	4.8	5.2	5.4	8.1	7.4
1995	4.9	5.2	5.4	8.3	7.3
1996	5.0	5.3	5.5	8.5	7.2
1997	5.0	5.3	5.5	8.6	7.2
1998	5.1	5.4	5.6	8.5	7.1
1999	5.2	5.4	5.6	8.5	7.1
2000	5.3	5.4	5.6	8.4	7.0
2001	5.4	5.5	5.7	8.3	6.9
2002	5.5	5.5	5.7	8.2	6.9
2003	5.6	5.6	5.8	8.1	6.8
2004	5.6	5.6	5.8	8.0	6.8
2005	5.7	5.7	5.9	8.0	6.7
APC0	**1.65***	0.79	0.75	0.57	**0.79***
APC1	–	–	–	**2.02***	**2.64***
APC2	–	–	–	-1.12	-0.81

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.21(a): PROSTATE (ICD-10 : C61) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

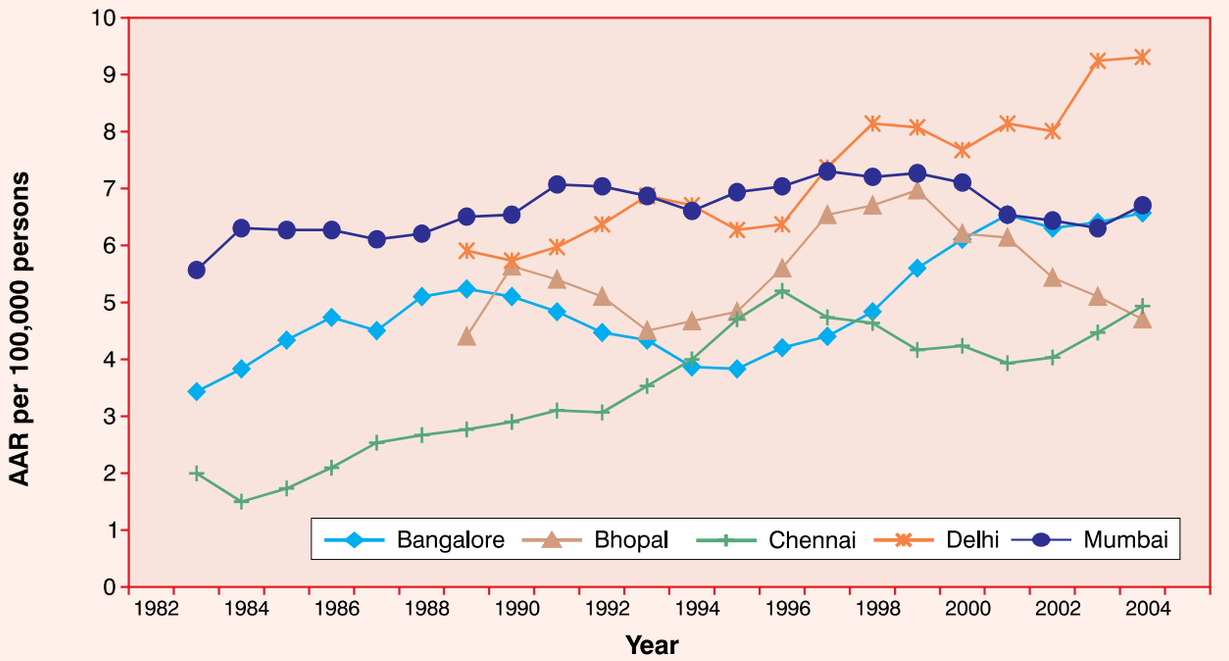


Table 4.21(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	3.7		2.8		5.1
1983	2.9		2.0		5.4
1984	3.7		1.2		6.2
1985	4.9		1.3		7.3
1986	4.4		2.7		5.3
1987	4.9		2.3		6.2
1988	4.2	1.9	2.6	6.3	6.8
1989	6.2	5.0	3.1	5.8	5.6
1990	5.3	6.3	2.6	5.6	7.1
1991	3.8	5.6	3.0	5.8	6.9
1992	5.4	4.3	3.7	6.5	7.2
1993	4.2	5.4	2.5	6.8	7.0
1994	3.4	3.8	4.4	7.3	6.4
1995	4.0	4.8	5.1	6.0	6.4
1996	4.1	5.9	4.6	5.5	8.0
1997	4.5	6.1	5.9	7.6	6.7
1998	4.6	7.6	3.7	9.0	7.2
1999	5.4	6.4	4.3	7.8	7.7
2000	6.8	6.9	4.5	7.4	6.9
2001	6.1	5.3	3.9	7.8	6.7
2002	6.7	6.2	3.4	9.2	6.0
2003	6.1	4.8	4.8	7.0	6.6
2004	6.4	4.3	5.2	11.5	6.3
2005	7.2	5.0	4.8	9.4	7.2
Slope(b)	**0.118**	**0.073**	**0.141**	**0.230**	**0.046**
p-value	**0.001**	0.221	**0.001**	**0.001**	**0.030**

Fig. 4.21(b): PROSTATE (ICD-10 : C61) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

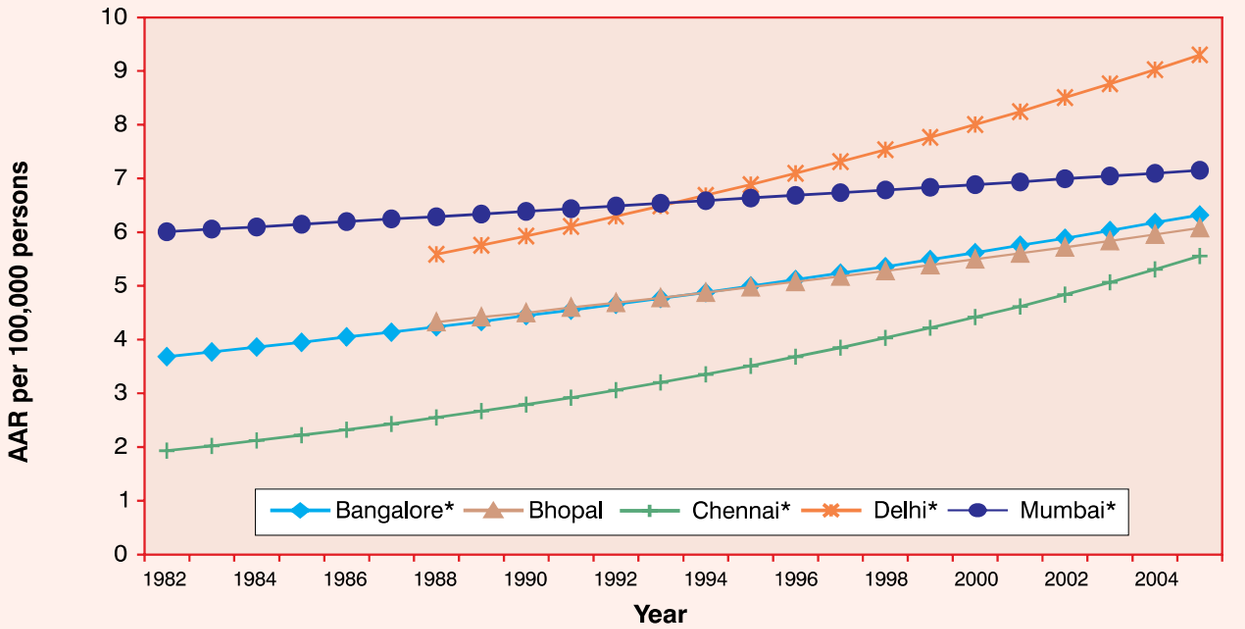


Table 4.21(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*	JP0*
1982	3.7		1.9		6.0
1983	3.8		2.0		6.1
1984	3.9		2.1		6.1
1985	3.9		2.2		6.1
1986	4.0		2.3		6.2
1987	4.1		2.4		6.2
1988	4.2	4.3	2.5	5.6	6.3
1989	4.3	4.4	2.7	5.8	6.3
1990	4.4	4.5	2.8	5.9	6.4
1991	4.5	4.6	2.9	6.1	6.4
1992	4.7	4.7	3.1	6.3	6.5
1993	4.8	4.8	3.2	6.5	6.5
1994	4.9	4.9	3.3	6.7	6.6
1995	5.0	5.0	3.5	6.9	6.6
1996	5.1	5.1	3.7	7.1	6.7
1997	5.2	5.2	3.8	7.3	6.7
1998	5.4	5.3	4.0	7.5	6.8
1999	5.5	5.4	4.2	7.8	6.8
2000	5.6	5.5	4.4	8.0	6.9
2001	5.8	5.6	4.6	8.2	6.9
2002	5.9	5.7	4.8	8.5	7.0
2003	6.0	5.8	5.1	8.8	7.0
2004	6.2	6.0	5.3	9.0	7.1
2005	6.3	6.1	5.6	9.3	7.2
APC0	2.38*	2.02	4.71*	3.05*	0.76*
APC1	–	–	–	–	–
APC2	–	–	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.22(a): BRAIN NERVOUS SYSTEM (ICD-10 : C70-72) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

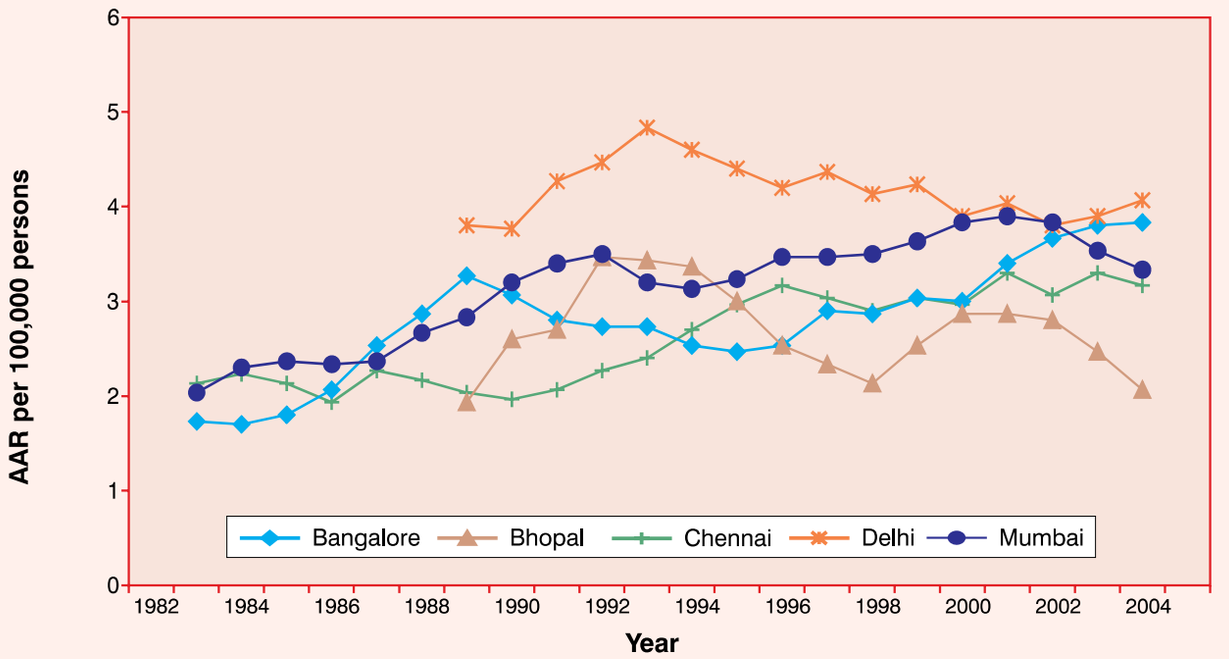


Table 4.22(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	1.6		1.2		1.8
1983	2.4		2.3		1.7
1984	1.0		2.9		2.6
1985	1.5		1.5		2.6
1986	2.7		2.0		1.9
1987	2.0		2.3		2.5
1988	2.9	0.9	2.5	3.8	2.7
1989	3.7	3.0	1.7	3.4	2.8
1990	3.2	1.9	1.9	4.2	3.0
1991	2.3	2.9	2.3	3.7	3.8
1992	2.9	3.3	2.0	4.9	3.4
1993	3.0	4.2	2.5	4.8	3.3
1994	2.3	2.8	2.7	4.8	2.9
1995	2.3	3.1	2.9	4.2	3.2
1996	2.8	3.1	3.3	4.2	3.6
1997	2.5	1.4	3.3	4.2	3.6
1998	3.4	2.5	2.5	4.7	3.2
1999	2.7	2.5	2.9	3.5	3.7
2000	3.0	2.6	3.7	4.5	4.0
2001	3.3	3.5	2.3	3.7	3.8
2002	3.9	2.5	3.9	3.9	3.9
2003	3.8	2.4	3.0	3.8	3.8
2004	3.7	2.5	3.0	4.0	2.9
2005	4.0	1.3	3.5	4.4	3.3
Slope(b)	**0.081**	**-0.012**	**0.069**	**-0.001**	**0.074**
p-value	**0.001**	0.764	**0.001**	0.969	**0.001**

Fig. 4.22(b): BRAIN, NERVOUS SYSTEM (ICD-10 : C70-72) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

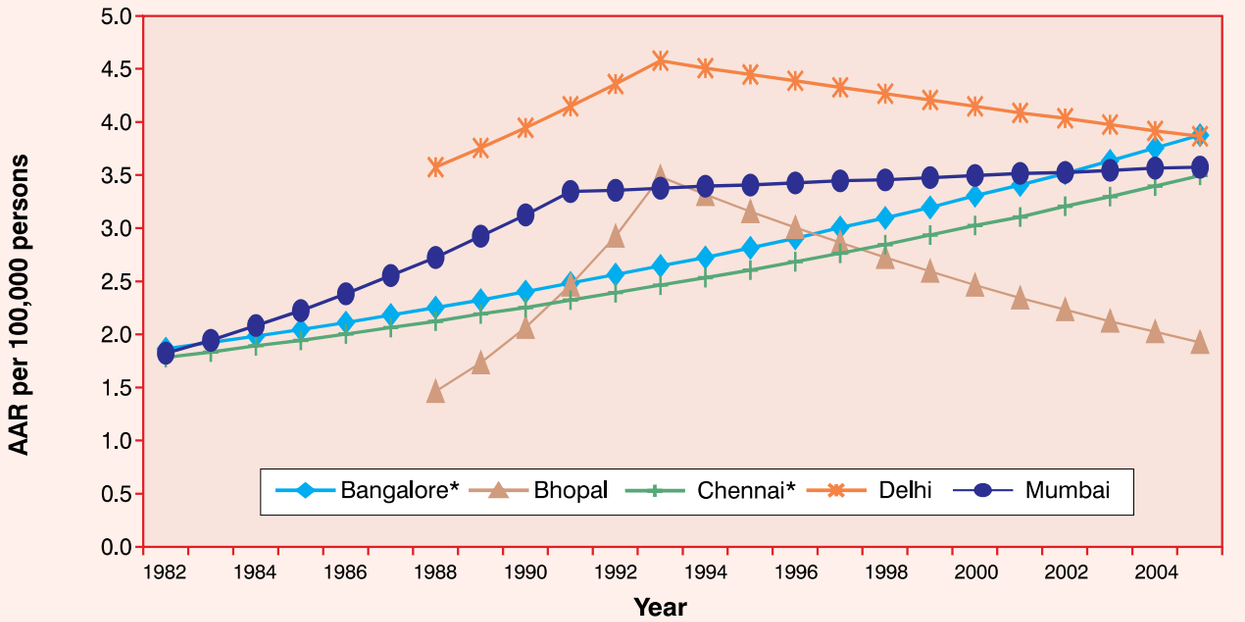


Table 4.22(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	**JP1***	**JP0***	**JP1***	**JP1***
1982	1.9		1.8		1.8
1983	1.9		1.8		1.9
1984	2.0		1.9		2.1
1985	2.0		1.9		2.2
1986	2.1		2.0		2.4
1987	2.2		2.1		2.6
1988	2.3	1.5	2.1	3.6	2.7
1989	2.3	1.7	2.2	3.8	2.9
1990	2.4	2.1	2.3	3.9	3.1
1991	2.5	2.5	2.3	4.1	**3.3**
1992	2.6	2.9	2.4	4.4	3.4
1993	2.6	**3.5**	2.5	**4.6**	3.4
1994	2.7	3.3	2.5	4.5	3.4
1995	2.8	3.2	2.6	4.4	3.4
1996	2.9	3.0	2.7	4.4	3.4
1997	3.0	2.9	2.8	4.3	3.4
1998	3.1	2.7	2.8	4.3	3.5
1999	3.2	2.6	2.9	4.2	3.5
2000	3.3	2.5	3.0	4.1	3.5
2001	3.4	2.3	3.1	4.1	3.5
2002	3.5	2.2	3.2	4.0	3.5
2003	3.6	2.1	3.3	4.0	3.5
2004	3.8	2.0	3.4	3.9	3.6
2005	3.9	1.9	3.5	3.9	3.6
APC0	**3.24***	0.01	**2.97***	0.00	**2.69***
APC1	–	19.07	–	5.04	**6.99***
APC2	–	-4.84	–	-1.39	0.49

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.23(a): BRAIN NERVOUS SYSTEM (ICD-10 : C70-72) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

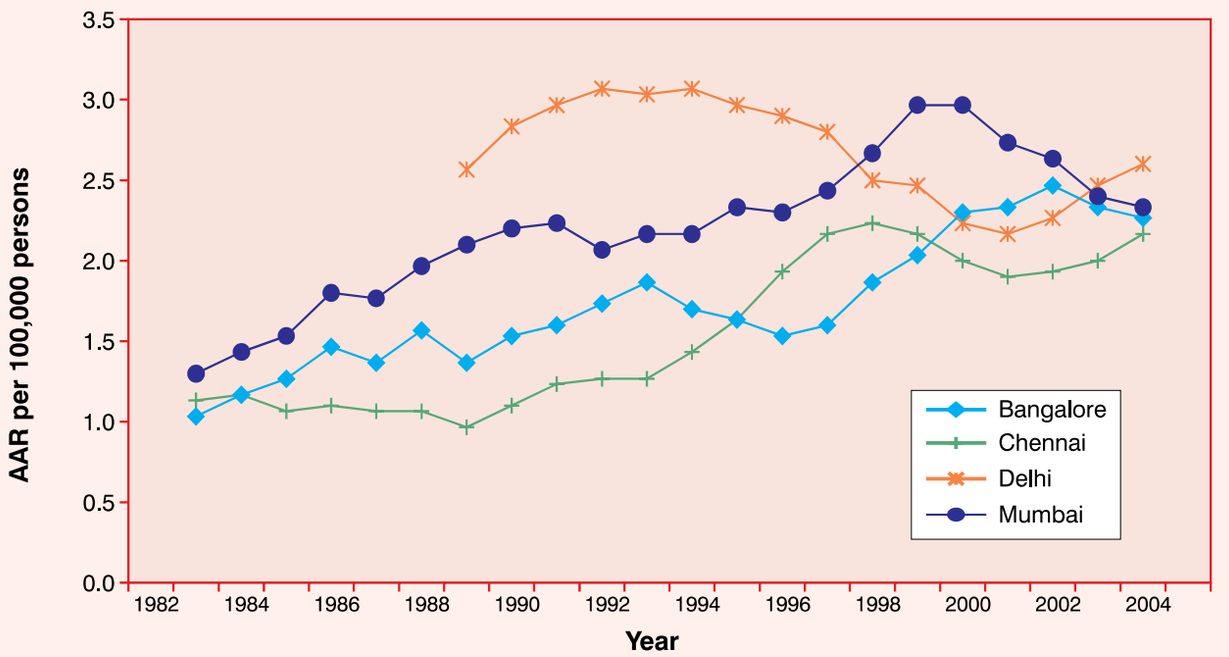


Table 4.23(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	1.1	0.8		1.3
1983	0.9	1.0		1.2
1984	1.1	1.6		1.4
1985	1.5	0.9		1.7
1986	1.2	0.7		1.5
1987	1.7	1.7		2.2
1988	1.2	0.8	2.0	1.6
1989	1.8	0.7	2.6	2.1
1990	1.1	1.4	3.1	2.6
1991	1.7	1.2	2.8	1.9
1992	2.0	1.1	3.0	2.2
1993	1.5	1.5	3.4	2.1
1994	2.1	1.2	2.7	2.2
1995	1.5	1.6	3.1	2.2
1996	1.3	2.1	3.1	2.6
1997	1.8	2.1	2.5	2.1
1998	1.7	2.3	2.8	2.6
1999	2.1	2.3	2.2	3.3
2000	2.3	1.9	2.4	3.0
2001	2.5	1.8	2.1	2.6
2002	2.2	2.0	2.0	2.6
2003	2.7	2.0	2.7	2.7
2004	2.1	2.0	2.7	1.9
2005	2.0	2.5	2.4	2.4
Slope	**0.054**	**0.063**	**-0.022**	**0.057**
p-value	**0.001**	**0.001**	0.229	**0.001**

Fig. 4.23(b): BRAIN NERVOUS SYSTEM (ICD-10 : C70-72) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

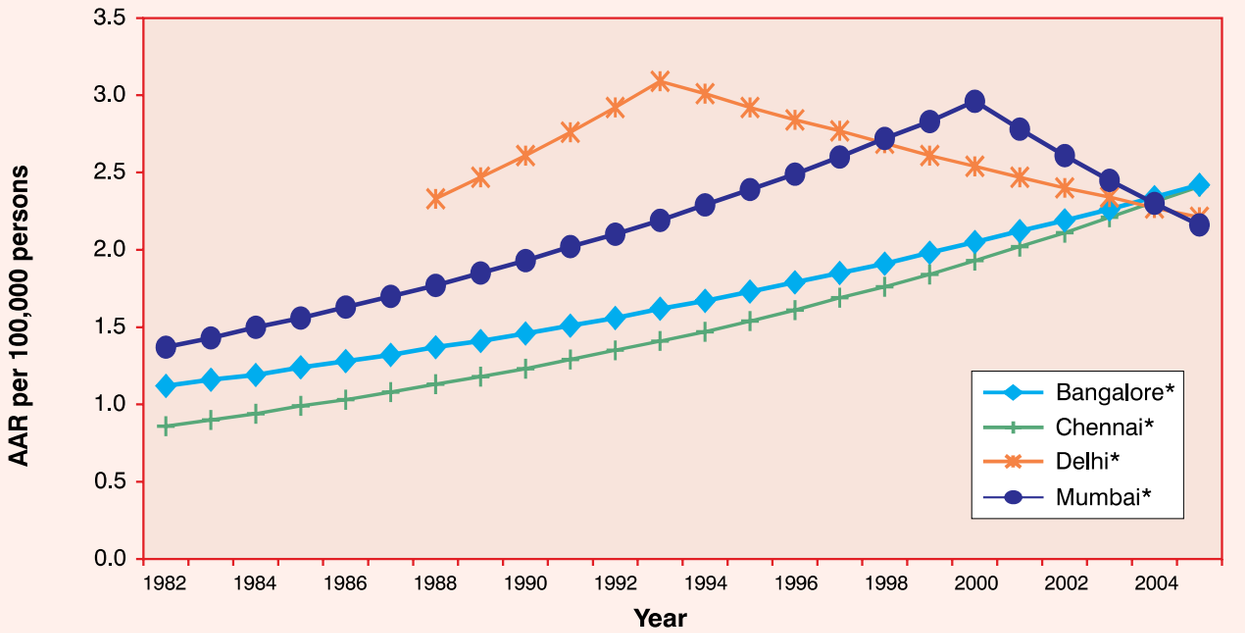


Table 4.23(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	**JP0***	**JP1***	**JP1***
1982	1.1	0.9		1.4
1983	1.2	0.9		1.4
1984	1.2	0.9		1.5
1985	1.2	1.0		1.6
1986	1.3	1.0		1.6
1987	1.3	1.1		1.7
1988	1.4	1.1	2.3	1.8
1989	1.4	1.2	2.5	1.9
1990	1.5	1.2	2.6	1.9
1991	1.5	1.3	2.8	2.0
1992	1.6	1.4	2.9	2.1
1993	1.6	1.4	**3.1**	2.2
1994	1.7	1.5	3.0	2.3
1995	1.7	1.5	2.9	2.4
1996	1.8	1.6	2.8	2.5
1997	1.9	1.7	2.8	2.6
1998	1.9	1.8	2.7	2.7
1999	2.0	1.8	2.6	2.8
2000	2.1	1.9	2.5	3.0
2001	2.1	2.0	2.5	2.8
2002	2.2	2.1	2.4	2.6
2003	2.3	2.2	2.3	2.5
2004	2.3	2.3	2.3	2.3
2005	2.4	2.4	2.2	2.2
APC0	**3.42***	**4.58***	-0.93	**2.90***
APC1	–	–	5.8	**4.35***
APC2	–	–	**-2.76***	-6.12

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.24(a): THYROID GLAND (ICD-10 : C73) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

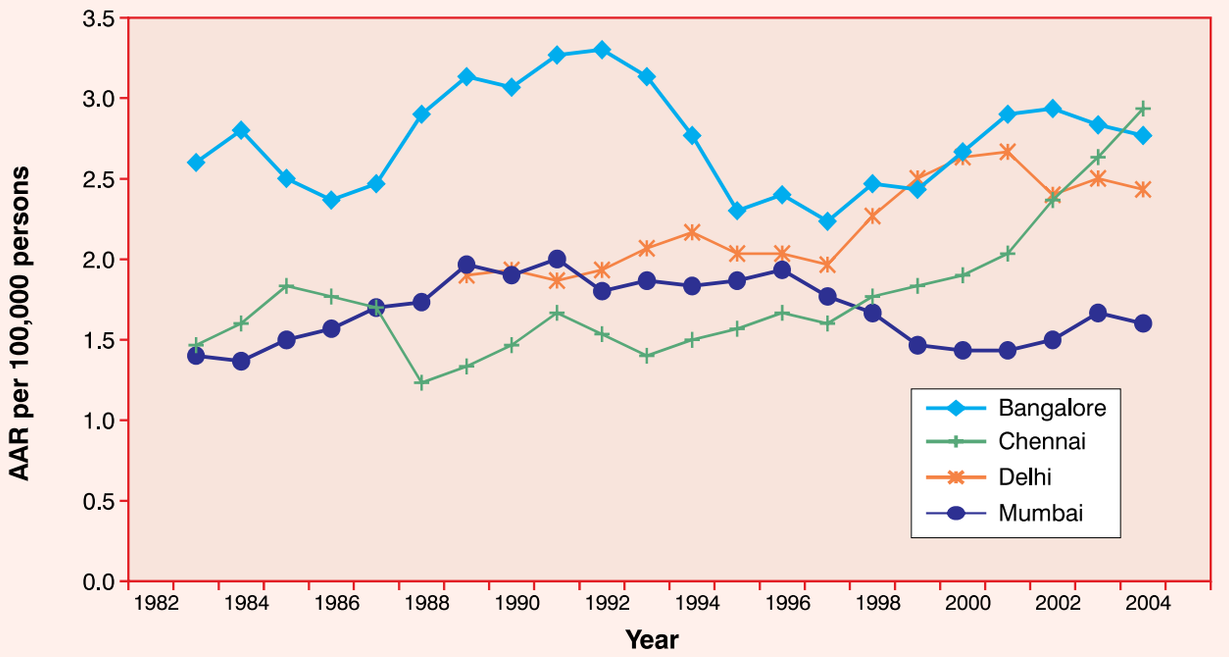


Table 4.24(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	2.2	1.3		1.5
1983	2.5	1.6		1.3
1984	3.1	1.5		1.4
1985	2.8	1.7		1.4
1986	1.6	2.3		1.7
1987	2.7	1.3		1.6
1988	3.1	1.5	1.7	1.8
1989	2.9	0.9	2.1	1.8
1990	3.4	1.6	1.9	2.3
1991	2.9	1.9	1.8	1.6
1992	3.5	1.5	1.9	2.1
1993	3.5	1.2	2.1	1.7
1994	2.4	1.5	2.2	1.8
1995	2.4	1.8	2.2	2.0
1996	2.1	1.4	1.7	1.8
1997	2.7	1.8	2.2	2.0
1998	1.9	1.6	2.0	1.5
1999	2.8	1.9	2.6	1.5
2000	2.6	2.0	2.9	1.4
2001	2.6	1.8	2.4	1.4
2002	3.5	2.3	2.7	1.5
2003	2.7	3.0	2.1	1.6
2004	2.3	2.6	2.7	1.9
2005	3.3	3.2	2.5	1.3
Slope	**0.005**	**0.050**	**0.049**	**0.000**
p-value	0.733	**0.001**	**0.001**	0.961

Fig. 4.24(b): THYROID GLAND (ICD-10 : C73) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

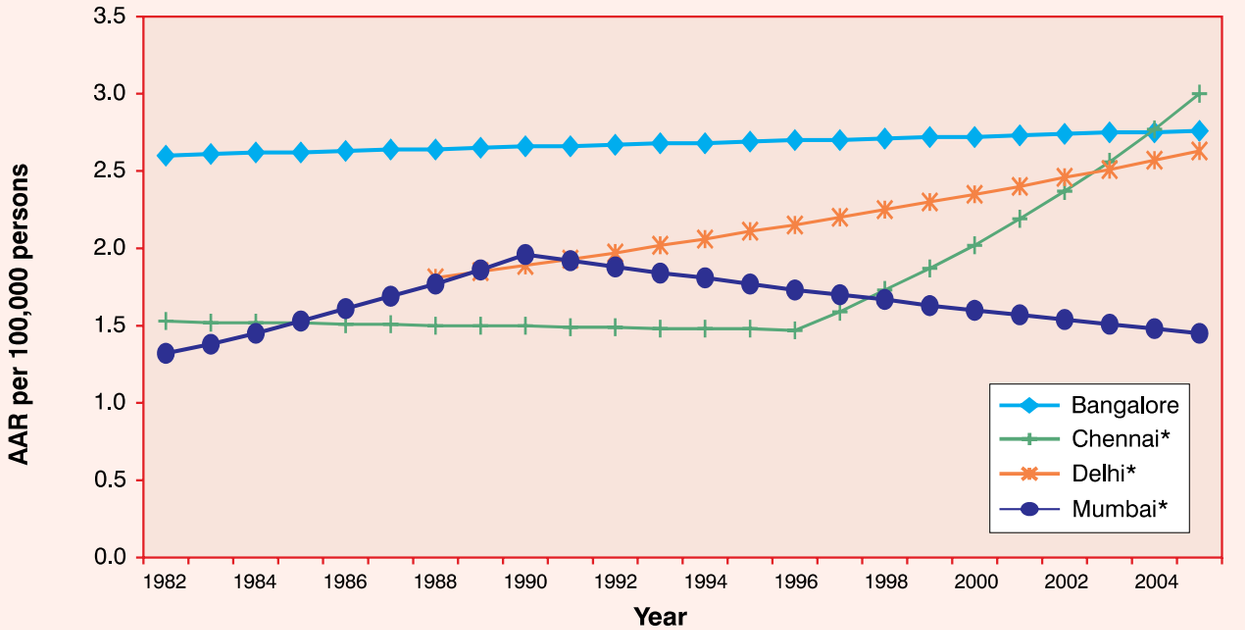


Table 4.24(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	**JP1***	**JP0***	**JP1***
1982	2.6	1.5		1.3
1983	2.6	1.5		1.4
1984	2.6	1.5		1.5
1985	2.6	1.5		1.5
1986	2.6	1.5		1.6
1987	2.6	1.5		1.7
1988	2.6	1.5	1.8	1.8
1989	2.7	1.5	1.9	1.9
1990	2.7	1.5	1.9	**2.0**
1991	2.7	**1.5**	1.9	1.9
1992	2.7	1.5	2.0	1.9
1993	2.7	1.5	2.0	1.8
1994	2.7	1.5	2.1	1.8
1995	2.7	1.5	2.1	1.8
1996	2.7	1.5	2.2	1.7
1997	2.7	1.6	2.2	1.7
1998	2.7	1.7	2.3	1.7
1999	2.7	1.9	2.3	1.6
2000	2.7	2.0	2.4	1.6
2001	2.7	2.2	2.4	1.6
2002	2.7	2.4	2.5	1.5
2003	2.8	2.6	2.5	1.5
2004	2.8	2.8	2.6	1.5
2005	2.8	3.0	2.6	1.5
APC0	0.26	**2.60***	**2.22***	-0.02
APC1	–	-0.26	–	**5.08***
APC2	**–**	**8.23***	**–**	**-2.00***

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.25(a): NHL (ICD-10 : C82-85,C96) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

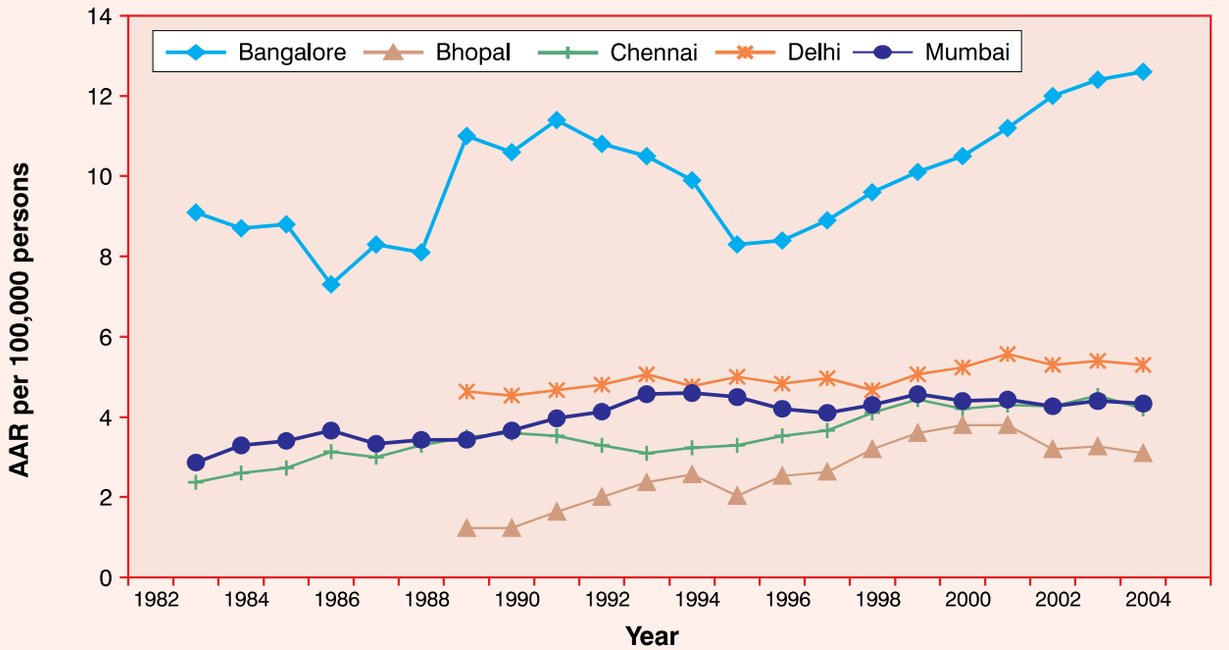


Table 4.25(a): Year wise AARs

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
1982	3.1		2.7		2.5
1983	2.9		2.2		3
1984	3.1		2.2		3.1
1985	2.7		3.4		3.8
1986	3.0		2.6		3.3
1987	1.6		3.4		3.9
1988	3.7	1.0	3.0	4.8	2.8
1989	2.8	0.6	3.5	4.8	3.6
1990	4.5	2.1	4.0	4.3	3.9
1991	3.3	1.0	3.3	4.5	3.5
1992	3.6	1.8	3.3	5.2	4.5
1993	3.9	3.2	3.3	4.7	4.4
1994	3.0	2.1	2.7	5.3	4.8
1995	3.0	2.4	3.7	4.3	4.6
1996	2.3	1.6	3.5	5.4	4.1
1997	3.1	3.6	3.4	4.8	3.9
1998	3.5	2.7	4.1	4.7	4.3
1999	3.0	3.3	4.8	4.5	4.7
2000	3.6	4.8	4.4	6.0	4.7
2001	3.9	3.3	3.4	5.2	3.8
2002	3.7	3.3	5.1	5.5	4.8
2003	4.4	3.0	4.3	5.2	4.2
2004	4.3	3.5	4.2	5.5	4.2
2005	3.9	2.8	4.1	5.2	4.6
Slope(b)	**0.047**	**0.149**	**0.082**	**0.047**	**0.070**
p-value	**0.014**	**0.001**	**0.001**	**0.023**	**0.001**

Fig. 4.25(b): NHL (ICD-10 : C82-85,C96) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

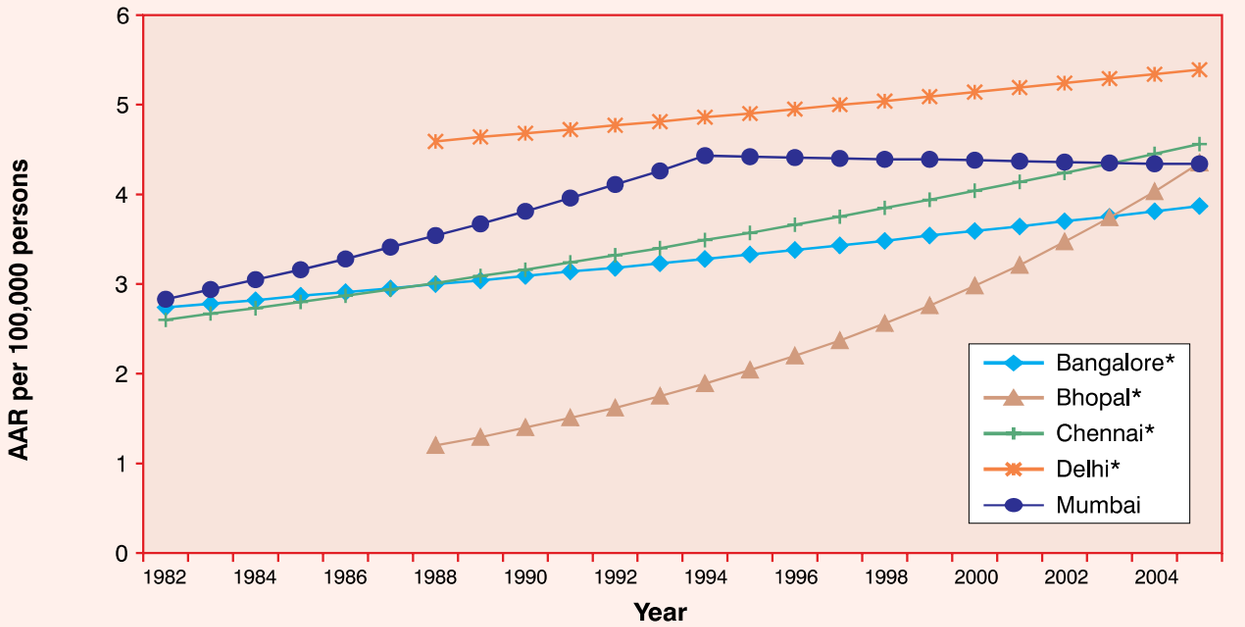


Table 4.25(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Bhopal	Chennai	Delhi	Mumbai
	JP0*	**JP0***	**JP0***	**JP0***	**JP1***
1982	2.7		2.6		2.8
1983	2.8		2.7		2.9
1984	2.8		2.7		3.1
1985	2.9		2.8		3.2
1986	2.9		2.9		3.3
1987	3.0		2.9		3.4
1988	3.0	1.2	3.0	4.6	3.5
1989	3.0	1.3	3.1	4.6	3.7
1990	3.1	1.4	3.2	4.7	3.8
1991	3.1	1.5	3.2	4.7	4.0
1992	3.2	1.6	3.3	4.8	4.1
1993	3.2	1.8	3.4	4.8	4.3
1994	3.3	1.9	3.5	4.9	**4.4**
1995	3.3	2.0	3.6	4.9	4.4
1996	3.4	2.2	3.7	5.0	4.4
1997	3.4	2.4	3.8	5.0	4.4
1998	3.5	2.6	3.9	5.0	4.4
1999	3.5	2.8	3.9	5.1	4.4
2000	3.6	3.0	4.0	5.1	4.4
2001	3.6	3.2	4.1	5.2	4.4
2002	3.7	3.5	4.2	5.2	4.4
2003	3.8	3.7	4.3	5.3	4.4
2004	3.8	4.0	4.5	5.3	4.3
2005	3.9	4.4	4.6	5.4	4.3
APC0	**1.51***	**7.87***	**2.47***	**0.95***	**1.91***
APC1	–	–	–	–	**3.80***
APC2	–	–	–	–	-0.19

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.26(a): NHL (ICD-10 : C82-85,C96) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

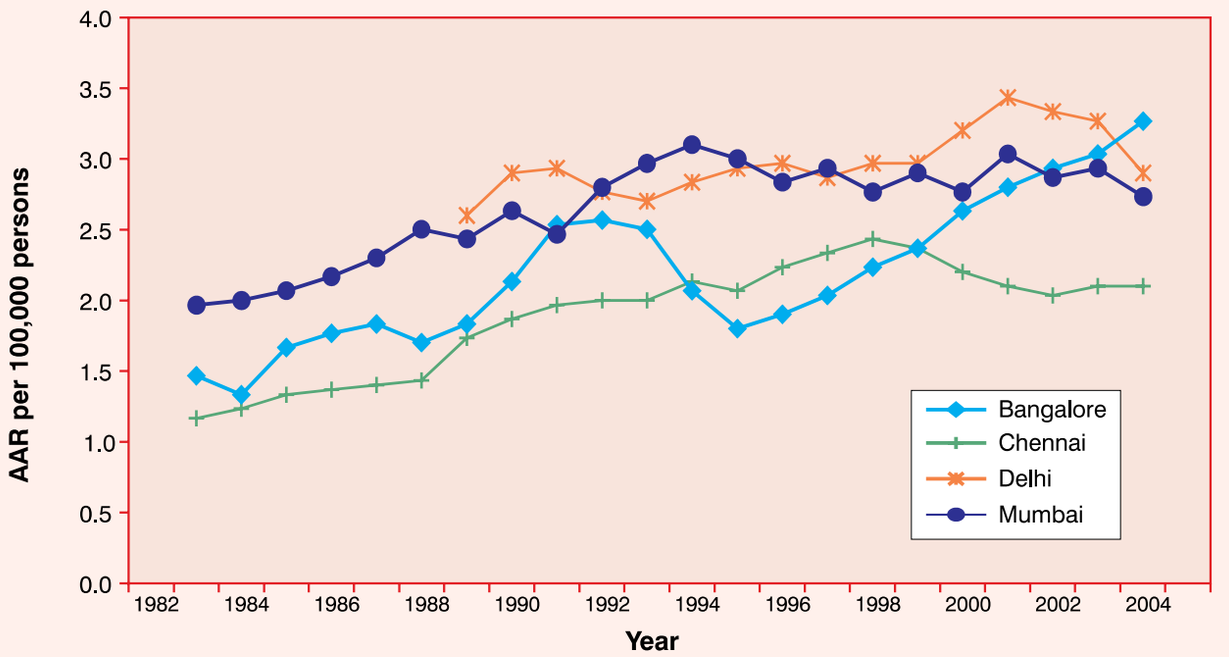


Table 4.26(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	1.4	1.3		1.8
1983	1.4	1.3		1.9
1984	1.6	0.9		2.2
1985	1.0	1.5		1.9
1986	2.4	1.6		2.1
1987	1.9	1.0		2.5
1988	1.2	1.6	2.3	2.3
1989	2.0	1.7	2.4	2.7
1990	2.3	1.9	3.1	2.3
1991	2.1	2.0	3.2	2.9
1992	3.2	2.0	2.5	2.2
1993	2.4	2.0	2.6	3.3
1994	1.9	2.0	3.0	3.4
1995	1.9	2.4	2.9	2.6
1996	1.6	1.8	2.9	3.0
1997	2.2	2.5	3.1	2.9
1998	2.3	2.7	2.6	2.9
1999	2.2	2.1	3.2	2.5
2000	2.6	2.3	3.1	3.3
2001	3.1	2.2	3.3	2.5
2002	2.7	1.8	3.9	3.3
2003	3.0	2.1	2.8	2.8
2004	3.4	2.4	3.1	2.7
2005	3.4	1.8	2.8	2.7
Slope	**0.075**	**0.048**	**0.034**	**0.043**
p-value	**0.001**	**0.001**	**0.044**	**0.001**

Fig. 4.26(b): NHL (ICD-10 : C82-85,C96) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

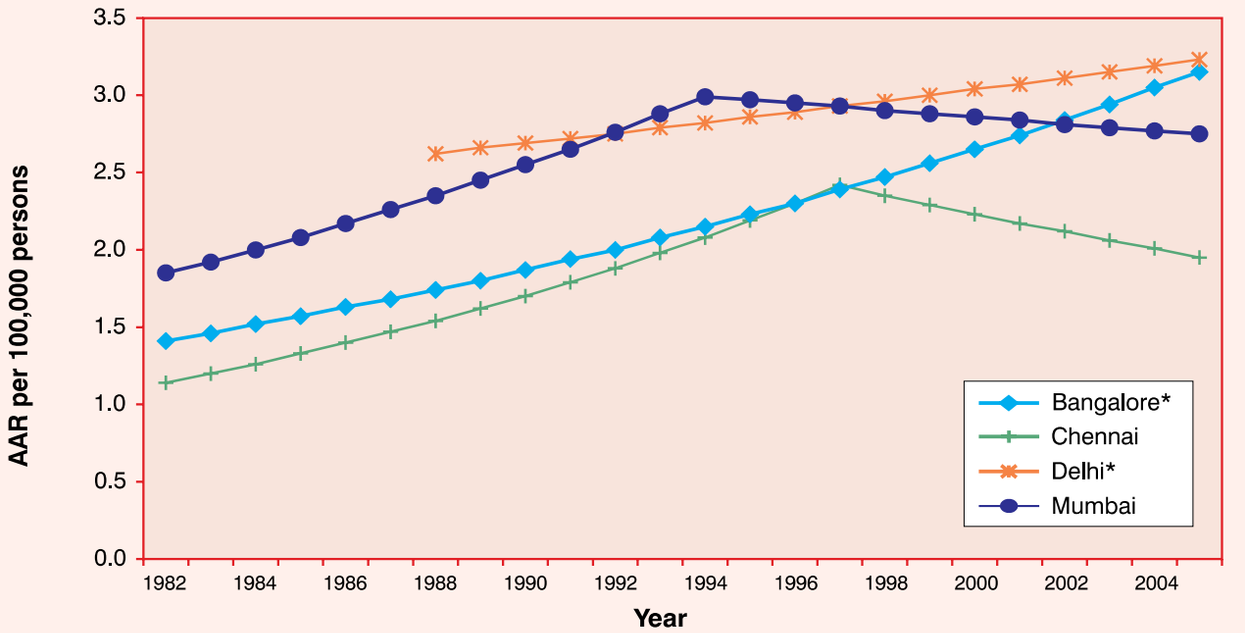


Table 4.26(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	**JP1***	**JP0***	**JP1***
1982	1.4	1.1		1.9
1983	1.5	1.2		1.9
1984	1.5	1.3		2.0
1985	1.6	1.3		2.1
1986	1.6	1.4		2.2
1987	1.7	1.5		2.3
1988	1.7	1.5	2.6	2.4
1989	1.8	1.6	2.7	2.5
1990	1.9	1.7	2.7	2.6
1991	1.9	1.8	2.7	2.7
1992	2.0	1.9	2.8	2.8
1993	2.1	2.0	2.8	2.9
1994	2.2	2.1	2.8	**3.0**
1995	2.2	2.2	2.9	3.0
1996	2.3	2.3	2.9	3.0
1997	2.4	**2.4**	2.9	2.9
1998	2.5	2.4	3.0	2.9
1999	2.6	2.3	3.0	2.9
2000	2.7	2.2	3.0	2.9
2001	2.7	2.2	3.1	2.8
2002	2.8	2.1	3.1	2.8
2003	2.9	2.1	3.2	2.8
2004	3.1	2.0	3.2	2.8
2005	3.2	2.0	3.2	2.8
APC0	**3.55***	**2.83***	**1.23***	**1.79***
APC1	**–**	**5.11***	**–**	**4.11***
APC2	–	-2.62	–	-0.78

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.27(a): LYMPHOID LEUKAEMIA (ICD-10 : C91) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

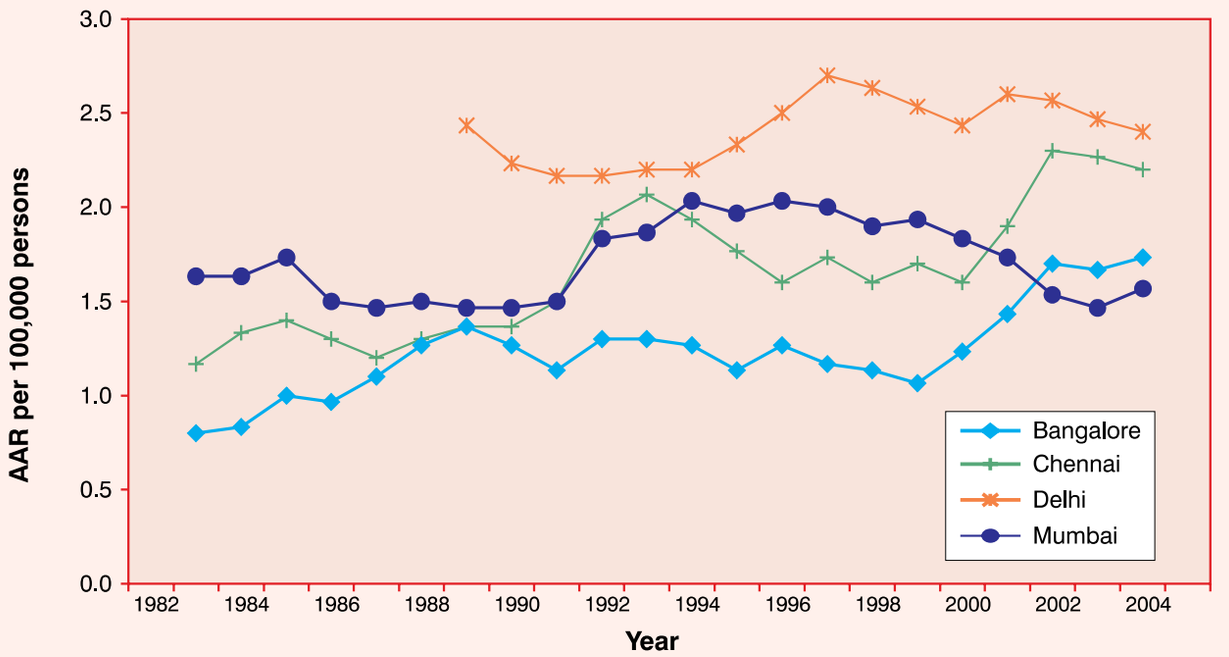


Table 4.27(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	0.8	1.2		1.7
1983	0.7	1.0		1.1
1984	0.9	1.3		2.1
1985	0.9	1.7		1.7
1986	1.2	1.2		1.4
1987	0.8	1.0		1.4
1988	1.3	1.4	2.8	1.6
1989	1.7	1.5	2.5	1.5
1990	1.1	1.2	1.9	1.3
1991	1.0	1.4	2.2	1.6
1992	1.3	1.9	2.3	1.6
1993	1.6	2.5	2.0	2.3
1994	1.0	1.8	2.3	1.7
1995	1.2	1.5	2.3	2.1
1996	1.2	2.0	2.4	2.1
1997	1.4	1.3	2.8	1.9
1998	0.9	1.9	2.9	2.0
1999	1.1	1.6	2.2	1.8
2000	1.2	1.6	2.5	2.0
2001	1.4	1.6	2.6	1.7
2002	1.7	2.5	2.7	1.5
2003	2.0	2.8	2.4	1.4
2004	1.3	1.5	2.3	1.5
2005	1.9	2.3	2.5	1.8
Slope(b)	**0.032**	**0.044**	**0.010**	**0.009**
p-value	**0.001**	**0.001**	0.451	0.316

Fig. 4.27(b): LYMPHOID LEUKAEMIA (ICD-10 : C91) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

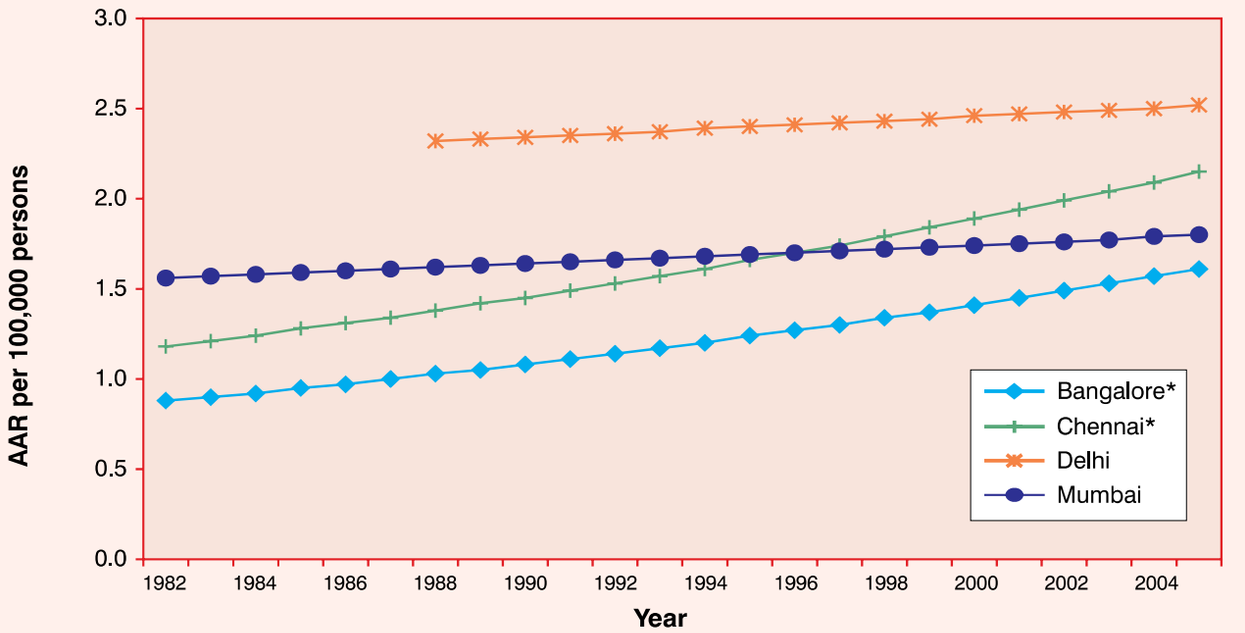


Table 4.27(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*
1982	0.9	1.2		1.6
1983	0.9	1.2		1.6
1984	0.9	1.2		1.6
1985	1.0	1.3		1.6
1986	1.0	1.3		1.6
1987	1.0	1.3		1.6
1988	1.0	1.4	2.3	1.6
1989	1.1	1.4	2.3	1.6
1990	1.1	1.5	2.3	1.6
1991	1.1	1.5	2.4	1.7
1992	1.1	1.5	2.4	1.7
1993	1.2	1.6	2.4	1.7
1994	1.2	1.6	2.4	1.7
1995	1.2	1.7	2.4	1.7
1996	1.3	1.7	2.4	1.7
1997	1.3	1.7	2.4	1.7
1998	1.3	1.8	2.4	1.7
1999	1.4	1.8	2.4	1.7
2000	1.4	1.9	2.5	1.7
2001	1.5	1.9	2.5	1.8
2002	1.5	2.0	2.5	1.8
2003	1.5	2.0	2.5	1.8
2004	1.6	2.1	2.5	1.8
2005	1.6	2.2	2.5	1.8
APC0	2.68*	2.64*	0.49	0.61
APC1	–	–	–	–
APC2	–	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.28(a): MYELOID LEUKAEMIA (ICD-10 : C92-94) - Males
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

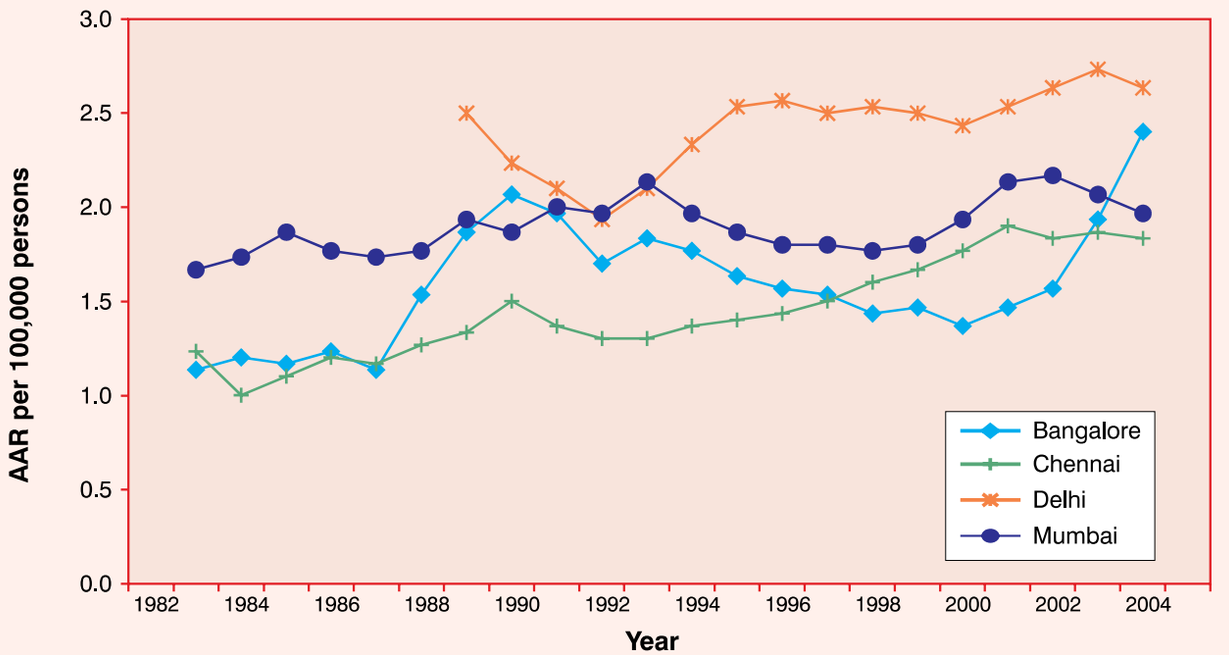


Table 4.28(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	1.0	1.7		1.6
1983	1.1	0.9		1.4
1984	1.3	1.1		2.0
1985	1.2	1.0		1.8
1986	1.0	1.2		1.8
1987	1.5	1.4		1.7
1988	0.9	0.9	2.8	1.7
1989	2.2	1.5	2.4	1.9
1990	2.5	1.6	2.3	2.2
1991	1.5	1.4	2.0	1.5
1992	1.9	1.1	2.0	2.3
1993	1.7	1.4	1.8	2.1
1994	1.9	1.4	2.5	2.0
1995	1.7	1.3	2.7	1.8
1996	1.3	1.5	2.4	1.8
1997	1.7	1.5	2.6	1.8
1998	1.6	1.5	2.5	1.8
1999	1.0	1.8	2.5	1.7
2000	1.8	1.7	2.5	1.9
2001	1.3	1.8	2.3	2.2
2002	1.3	2.2	2.8	2.3
2003	2.1	1.5	2.8	2.0
2004	2.4	1.9	2.6	1.9
2005	2.7	2.1	2.5	2.0
Slope(b)	**0.034**	**0.036**	**0.021**	**0.014**
p-value	**0.018**	**0.001**	0.107	**0.034**

Fig. 4.28(b): MYELOID LEUKAEMIA (ICD-10 : C92-94) - Males
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

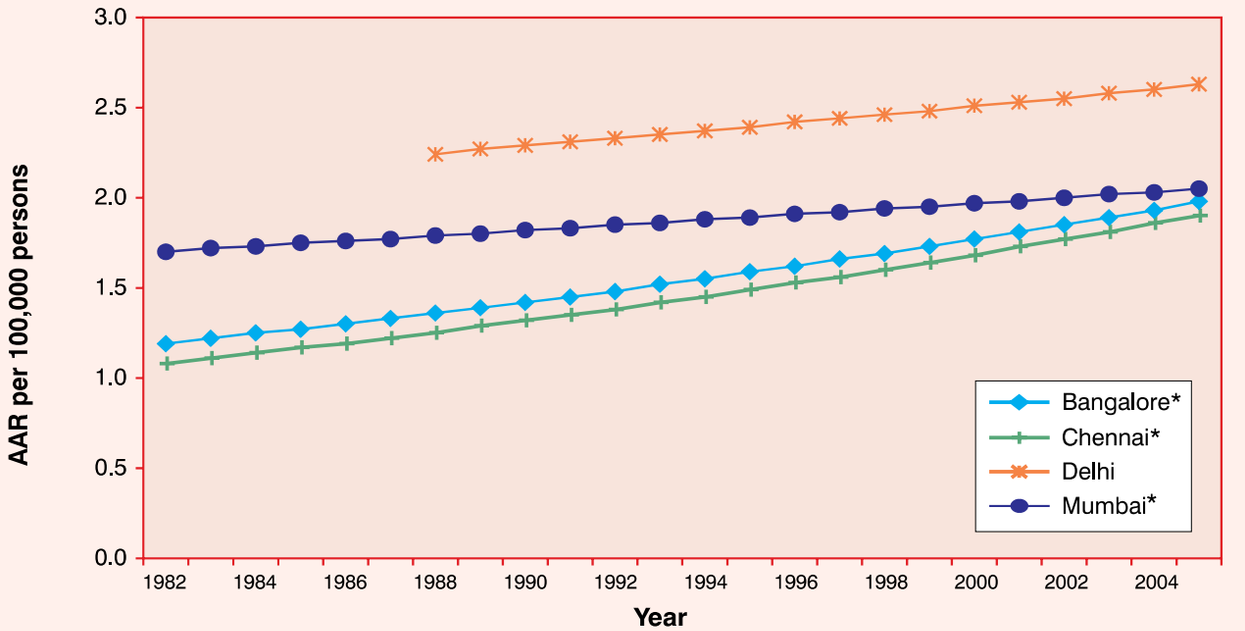


Table 4.28(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*
1982	1.2	1.1		1.7
1983	1.2	1.1		1.7
1984	1.3	1.1		1.7
1985	1.3	1.2		1.8
1986	1.3	1.2		1.8
1987	1.3	1.2		1.8
1988	1.4	1.3	2.2	1.8
1989	1.4	1.3	2.3	1.8
1990	1.4	1.3	2.3	1.8
1991	1.5	1.4	2.3	1.8
1992	1.5	1.4	2.3	1.9
1993	1.5	1.4	2.4	1.9
1994	1.6	1.5	2.4	1.9
1996	1.6	1.5	2.4	1.9
1997	1.7	1.6	2.4	1.9
1998	1.7	1.6	2.5	1.9
1999	1.7	1.6	2.5	1.9
2000	1.8	1.7	2.5	2.0
2001	1.8	1.7	2.5	2.0
2002	1.9	1.8	2.6	2.0
2003	1.9	1.8	2.6	2.0
2004	1.9	1.9	2.6	2.0
2005	2.0	1.9	2.6	2.1
APC0	2.23*	2.49*	0.93	0.80*
APC1	–	–	–	–
APC2	–	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Fig. 4.29(a): MYELOID LEUKAEMIA (ICD-10 : C92-94) - Females
Trends over time (1982-2005) in AAR *(Three Year Moving Average)*

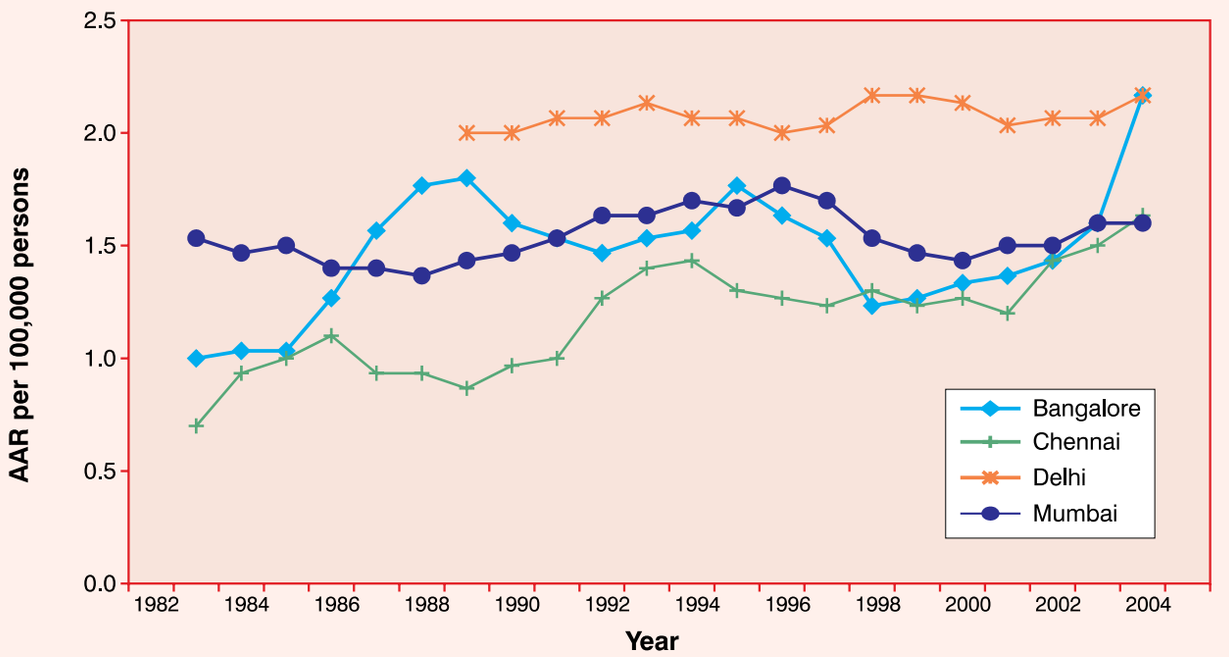


Table 4.29(a): Year wise AARs

Year	Bangalore	Chennai	Delhi	Mumbai
1982	1.0	0.4		1.6
1983	1.2	0.9		1.3
1984	0.8	0.8		1.7
1985	1.1	1.1		1.4
1986	1.2	1.1		1.4
1987	1.5	1.1		1.4
1988	2.0	0.6	2.0	1.4
1989	1.8	1.1	2.0	1.3
1990	1.6	0.9	1.4	1.6
1991	1.4	0.9	1.9	1.5
1992	1.6	1.2	2.2	1.5
1993	1.4	1.7	1.6	1.9
1994	1.6	1.3	2.2	1.5
1995	1.7	1.3	2.0	1.7
1996	2.0	1.3	1.9	1.8
1997	1.2	1.2	1.9	1.8
1998	1.4	1.2	2.1	1.5
1999	1.1	1.5	2.4	1.3
2000	1.3	1.0	1.8	1.6
2001	1.6	1.3	1.7	1.4
2002	1.2	1.3	2.1	1.5
2003	1.5	1.7	2.1	1.6
2004	2.1	1.5	1.7	1.7
2005	2.9	1.7	2.4	1.5
Slope	**0.030**	**0.035**	**0.012**	**0.005**
p-value	**0.020**	**0.001**	0.302	0.285

Fig. 4.29(b): MYELOID LEUKAEMIA (ICD-10 : C92-94) - Females
Trends over time (1982-2005) in AAR *(Joinpoint Regression Model)*

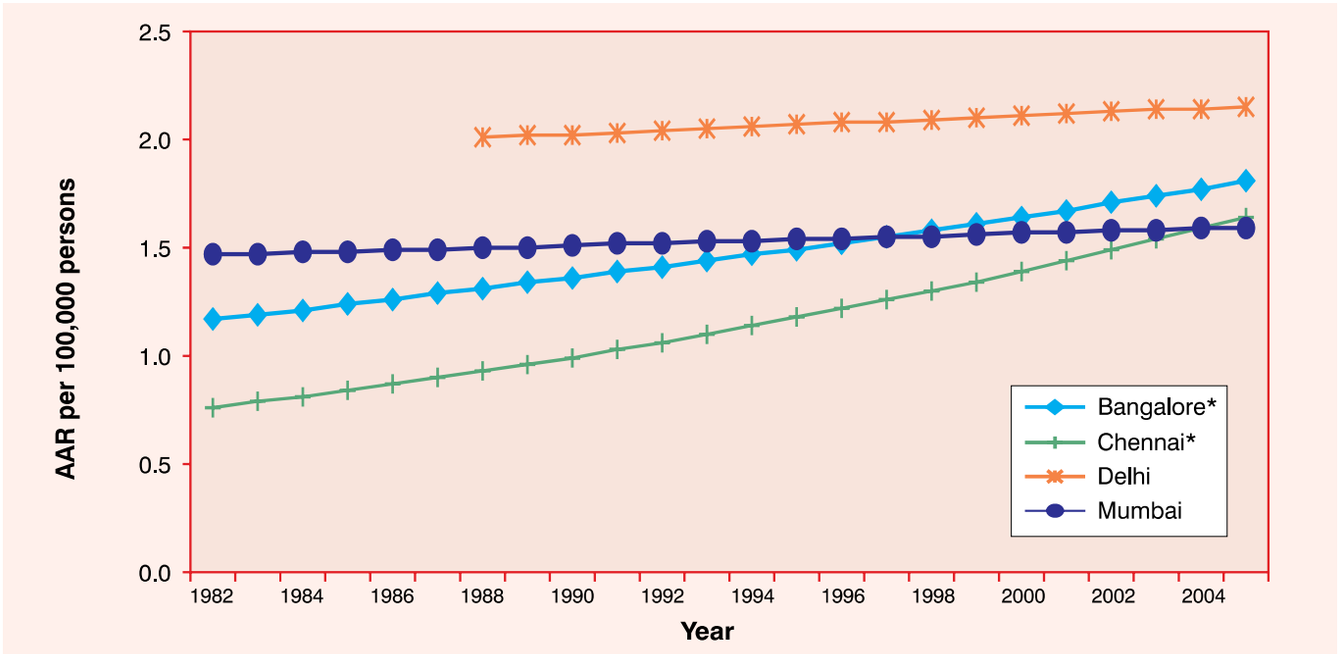


Table 4.29(b): Value of Joinpoint AARs with Annual Percent Change (APC)

Year	Bangalore	Chennai	Delhi	Mumbai
	JP0*	JP0*	JP0*	JP0*
1982	1.2	0.8		1.5
1983	1.2	0.8		1.5
1984	1.2	0.8		1.5
1985	1.2	0.8		1.5
1986	1.3	0.9		1.5
1987	1.3	0.9		1.5
1988	1.3	0.9	2.0	1.5
1989	1.3	1.0	2.0	1.5
1990	1.4	1.0	2.0	1.5
1991	1.4	1.0	2.0	1.5
1992	1.4	1.1	2.0	1.5
1993	1.4	1.1	2.1	1.5
1994	1.5	1.1	2.1	1.5
1995	1.5	1.2	2.1	1.5
1996	1.5	1.2	2.1	1.5
1997	1.6	1.3	2.1	1.6
1998	1.6	1.3	2.1	1.6
1999	1.6	1.3	2.1	1.6
2000	1.6	1.4	2.1	1.6
2001	1.7	1.4	2.1	1.6
2002	1.7	1.5	2.1	1.6
2003	1.7	1.5	2.1	1.6
2004	1.8	1.6	2.1	1.6
2005	1.8	1.6	2.2	1.6
APC0	1.90*	3.41*	0.41	0.36
APC1	–	–	–	–
APC2	–	–	–	–

*Values of years where a shift in trend observed is highlighted; * represents significant Joinpoint Model & APC ($p<0.05$) values.*

Chapter 5

PROJECTION OF BURDEN OF CANCER

Projection of cancer burden means a systematic way of prediction of number of cancer cases for all anatomical sites or for a specific site and for a specified period of time. This could be based on time trend in incidence rates based on the projected population.

The present chapter projects the cancer cases for the country by sex for selected sites of cancer for the periods 2008-2010, 2015 & 2020 [Table 5(a) and 5(b)]. The incidence data generated by PBCRs at Bangalore, Barshi, Bhopal, Chennai, Delhi and Mumbai for the years 2001-2005 formed the sources of data. The Crude Incidence Rate (CR) was considered suitable for assessing the future load (magnitude) of cancer cases in the country. The CR is preferable to AAR as the latter is more suitable for comparison of rates between areas than for assessing the disease burden for the area. The combination of time trend in pooled crude rates of selected sites for past five years and population estimate by time was used to arrive at the projection for each of the above periods. The Linear Regression method was used to assess the time trend. For whichever sites the trend was not found to be significant, the latest rates were taken into consideration.

The pooled crude rates of the five urban registries (Bangalore, Barshi, Chennai, Delhi and Mumbai) were taken to represent the estimates for all Indian states excluding states from the North East region. The Crude Rate of various cancer sites provided in the report of 2005-2006 for the North East region were assumed to represent the estimates for the same area. The crude rate of cancers of cervix and breast of the rural registry at Barshi was taken into account to represent the rural areas of India. Accordingly, the weightage of 0.7 and 0.3 for rural and urban areas respectively was used to estimate the projection for Breast and Cervix cancers.

The Percentage change observed in decadal growth rate of 1991-2001 as compared to the decadal growth of 1981-1991 was assumed to continue and correspondingly the growth rate of India is calculated separately for both males and females to calculate the yearly populations for the year 2001-2020.

Table 5(a): Projected Cases at India level for Selected Sites and Selected time periods (2008-2010, 2015, 2020) - MALES

ICD-10	Site Name	2008	2009	2010	2015	2020
C00-C96	**All Sites**	**447399**	**454842**	**462408**	**497081**	**534354**
C01-C02	**Tongue**	23932	24330	24735	26590	28584
C03-C06	**Mouth**	28066	29474	30921	38380	46785
C12-C13	**Hypopharynx**	14131	14366	14605	15700	16878
C15	**Oesophagus**	23573	23433	23281	22114	20642
C16	**Stomach**	24993	25408	25831	27768	29850
C18	**Colon**	11236	11423	11613	12484	13420
C19-C20	**Rectum**	11738	11933	12132	13041	14019
C22	**Liver**	14062	14295	14533	15623	16795
C23-C24	**Gall Bladder**	8396	8536	8678	9329	10028
C32	**Larynx**	24356	24761	25173	27060	29089
C33-C34	**Lung**	42863	43576	44301	47623	51194
C61	**Prostate**	25273	25693	26120	28079	30185
C70-C72	**Brain NS**	18238	18541	18850	20263	21782
C82-C95, C96	**NHL**	19835	20165	20501	22038	23690
C91	**Lymp. Leuk.**	9565	9724	9886	10627	11424
C92-C94	**Myeloid Leuk.**	11616	11809	12005	12905	13873

Table 5(b): Projected Cases at India level for Selected Sites and Selected time periods (2008-2010, 2015, 2020) - FEMALES

ICD-10	Site Name	2008	2009	2010	2015	2020
C00-C96	**All Sites**	**498773**	**507990**	**517378**	**563808**	**614404**
C01-C02	**Tongue**	7687	7829	7974	8689	9469
C03-C06	**Mouth**	14402	14669	14940	16280	17741
C12-C13	**Hypopharynx**	4620	4706	4793	5223	5691
C15	**Oesophagus**	17755	18083	18417	20070	21871
C16	**Stomach**	12458	12689	12923	14083	15347
C18	**Colon**	10675	11276	11896	15206	19014
C19-C20	**Rectum**	9005	9172	9341	10180	11093
C22	**Liver**	7564	7943	8334	10412	12795
C23-C24	**Gall Bladder**	17839	18169	18505	20166	21975
C32	**Larynx**	3894	3966	4039	4401	4796
C33-C34	**Lung**	13009	13250	13494	14705	16025
C50	**Breast**	84805	87693	90659	106124	123634
C53	**Cervix**	100088	101938	103821	113138	123291
C54	**Corpus Uteri**	14314	14579	14848	16181	17633
C56	**Ovary**	29386	29929	30482	33218	36199
C70-C72	**Brain NS**	11232	11440	11651	12697	13836
C73	**Thyroid Gland**	11329	11538	11751	12806	13955
C82-C85, C96	**NHL**	11696	11913	12133	13222	14408
C91	**Lymp. Leuk.**	5703	5808	5916	6447	7025
C92-C94	**Myeloid Leuk.**	11070	11770	12492	16363	20828

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ANNEXURE P/3

REPORT NO. 72

सत्यमेव जयते

PARLIAMENT OF INDIA
RAJYA SABHA

DEPARTMENT-RELATED PARLIAMENTARY STANDING COMMITTEE ON HEALTH AND FAMILY WELFARE

SEVENTY-SECOND REPORT

On

ALLEGED IRREGULARITIES IN THE CONDUCT OF STUDIES USING HUMAN PAPILLOMA VIRUS (HPV) VACCINE BY PATH IN INDIA

(DEPARTMENT OF HEALTH RESEARCH, MINISTRY OF HEALTH AND FAMILY WELFARE)

(*Presented to the Rajya Sabha on* 30th August, 2013)

(*Laid on the Table of Lok Sabha on 30th August,* 2013)

Rajya Sabha Secretariat, New Delhi
August, 2013/Bhadra, 1935 (SAKA)

सत्यमेव जयते

PARLIAMENT OF INDIA

RAJYA SABHA

DEPARTMENT-RELATED PARLIAMENTARY STANDING COMMITTEE

SEVENTY-SECOND REPORT

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(DEPARTMENT OF HEALTH RESEARCH, MINISTRY OF HEALTH AND FAMILY WELFARE)

(*Presented to the Rajya Sabha on* 30th August, 2013)

(*Laid on the Table of Lok Sabha on* 30th August, 2013)

ON HEALTH AND FAMILY WELFARE

Rajya Sabha Secretariat, New Delhi
August, 2013/Bhadra, 1935 (SAKA)

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COMPOSITION OF THE COMMITTEE
(2009-10)

RAJYA SABHA

1. Shri Amar Singh - **Chairman**
2. Shrimati Viplove Thakur
3. Dr. Radhakant Nayak
4. Shri Janardan Dwivedi
5. Shri Balbir Punj
6. Dr. Prabhakar Kore
7. Shrimati Brinda Karat
8. Shrimati Vasanthi Stanley
9. Dr. M.A.M. Ramaswamy
10. Dr. Anbumani Ramadoss

LOK SABHA

11. Shri J. M. Aaron Rashid
12. Shri Ashok Argal
13. Shrimati Sarika Devendra Singh Baghel
14. Shri Vijay Bahuguna
15. Dr. Chinta Mohan
16. Shrimati Tabassum Hasan
17. Dr. Sanjay Jaiswal
18. Shri S. R. Jeyadurai
19. Dr. (Shrimati) Kruparani Killi
20. Shri N. Kristappa
21. Dr. Tarun Mandal
22. Shri Datta Meghe
23. Dr. Jyoti Mirdha
24. Shrimati Jayshreeben Patel
25. Shri R.K. Singh Patel
26. Shri M. K Raghavan
27. Dr. Anup Kumar Saha
28. Shrimati Meena Singh
29. Dr. Arvind Kumar Sharma
30. Shri Pradeep Kumar Singh
31. Shri Ratan Singh

SECRETARIAT

Shrimati Vandana Garg	Joint Secretary
Shri R. B. Gupta	Director
Shrimati Arpana Mendiratta	Joint Director
Shri Dinesh Singh	Committee Officer

COMPOSITION OF THE COMMITTEE
(2010-2011)

RAJYA SABHA

1. Shri Brajesh Pathak **- Chairman**
2. Shri Janardan Dwivedi
3. Shrimati Viplove Thakur
4. Dr. Vijaylaxmi Sadho
5. Shri Balbir Punj
6. Dr. Prabhakar Kore
@7. Shrimati Brinda Karat
8. Shrimati Vasanthi Stanley
9. Shri Rasheed Masood
*10. Shrimati B. Jayashree

LOK SABHA

11. Shri Ashok Argal
12. Shrimati Sarika Devendra Baghel Singh
13. Shri Vijay Bahuguna
14. Shrimati Tabassum Hasan
15. Dr. Sanjay Jaiswal
16. Shri S. R. Jeyadurai
17. Dr. Kruparani Killi
18. Shri Nimmala Kristappa
19. Dr. Tarun Mandal
20. Shri Datta Meghe
21. Dr. Jyoti Mirdha
22. Dr. Chinta Mohan
23. Shrimati Jayshreeben Patel
24. Shri R.K. Singh Patel
25. Shri M. K Raghavan
26. Shri J. M. Aaron Rashid
27. Dr. Anup Kumar Saha
28. Dr. Arvind Kumar Sharma
29. Shrimati Meena Singh
30. Shri Pradeep Kumar Singh
31. Shri Ratan Singh

SECRETARIAT

Shrimati Vandana Garg, Additional Secretary
Shri R.B.Gupta, Director
Shrimati Arpana Mendiratta, Joint Director
Shri Dinesh Singh, Assistant Director
Shri Satis Mesra Committee Officer

---

* nominated to the Committee w.e.f 21/9/2010.
@ceased to be a member w.e.f 18th August, 2011.

COMPOSITION OF THE COMMITTEE
(2011-12)

RAJYA SABHA

1. Shri Brajesh Pathak - Chairman
*2 Shri Janardhan Dwivedi
%3. Shrimati Viplove Thakur
4. Dr. Vijaylaxmi Sadho
5. Shri Balbir Punj
6. Dr. Prabhakar Kore..
7. Shrimati Vasanthi Stanley
^ 8. Shri Rasheed Masood
9. Shrimati B. Jayashree
10. Shri Derek O'Brien

LOK SABHA

11. Shri Ashok Argal
&&12. Shrimati Harsimrat Kaur Badal
@ 13. Shri Vijay Bahuguna
14. Shrimati Raj Kumari Chauhan
15. Shrimati Bhavana Gawali
16. Dr. Sucharu Ranjan Haldar
17. Dr. Monazir Hassan
18. Dr. Sanjay Jaiswal
19. Shri S. R. Jeyadurai
20. Shri P. Lingam
21. Shri Datta Meghe
22. Dr. Jyoti Mirdha
23. Dr. Chinta Mohan
24. Shri Sidhant Mohapatra
25. Shrimati Jayshreeben Kanubhai Patel
26. Shri M. K Raghavan
27. Shri J. M. Aaron Rashid
28. Dr. Arvind Kumar Sharma
29. Shri Radhe Mohan Singh
30. Shri Ratan Singh
31. Dr. Kirit Premjibhai Solanki

SECRETARIAT

Shrimati Vandana Garg	Joint Secretary
Shri R. B. Gupta	Director
Shrimati Arpana Mendiratta	Joint Director
Shri Dinesh Singh	Deputy Director

---

* ceased to be a Member w.e.f 27th January, 2012 and re-nominated to the Committee on 2nd February, 2012
% Vacant vide resignation w.e.f. 2nd April, 2012.
^ Vacant vide resignation w.e.f 9th March, 2012 and renominated as Member w.e.f 04th May, 2012 and Member of Sub Committee II on CGHS W.E.F. 01st June,2012.
&& ceased to be a member w.e.f 29th June, 20112
@ vacant vide resignation w.e.f. 30th April, 2012

COMPOSITION OF THE COMMITTEE ON HEALTH AND FAMILY WELFARE
(2012-13)

RAJYA SABHA

1.	Shri Brajesh Pathak	-	**Chairman**
2.	Dr. Vijaylaxmi Sadho		
*3.	Dr. K. Chiranjeevi		
4.	Shri Rasheed Masood		
5.	Dr. Prabhakar Kore		
6.	Shri Jagat Prakash Nadda		
7.	Shri Arvind Kumar Singh		
&8.	Shri D. Raja		
9.	Shri H. K. Dua		
10.	Shrimati B. Jayashree		

LOK SABHA

@11.	Shri Ashok Argal
12.	Shri Kirti Azad
13.	Shri Mohd. Azharuddin
14.	Shrimati Sarika Devendra Singh Baghel
15.	Shri Kuvarjibhai M. Bavalia
16.	Shrimati Priya Dutt
17.	Dr. Sucharu Ranjan Haldar
18.	Mohd. Asrarul Haque
19.	Dr. Monazir Hassan
20.	Dr. Sanjay Jaiswal
21.	Dr. Tarun Mandal
22.	Shri Mahabal Mishra
23.	Shri Zafar Ali Naqvi
24.	Shrimati Jayshreeben Patel
25.	Shri Harin Pathak
26.	Shri Ramkishun
27.	Dr. Anup Kumar Saha
28.	Dr. Arvind Kumar Sharma
29.	Dr. Raghuvansh Prasad Singh
30.	Shri P.T. Thomas
#31.	Shri Chowdhury Mohan Jatua

SECRETARIAT

Shri P.P.K. Ramacharyulu	Joint Secretary
Shri R. B. Gupta	Director
Shrimati Arpana Mendiratta	Joint Director
Shri Dinesh Singh	Deputy Director
Shri Pratap Shenoy	Committee Officer

---

* ceased to be Member of the Committee w.e.f. 28th October, 2012.
@ ceased to be Member of the Committee w.e.f. 9th January, 2013.
nominated as a Member to the Committee w.e.f. 14th December, 2012.
& ceased to be Member of the Committee w.e.f. 24th July, 2013..

PREFACE

I, the Chairman of the Department-related Parliamentary Standing Committee on Health and Family Welfare, having been authorized by the Committee to present the Report on its behalf, do hereby present this Seventy-Second Report of the Committee on the "Alleged Irregularities in the Conduct of Studies Using Human Papilloma Virus (HPV) Vaccine" by Programme for Appropriate Technology in Health(PATH) in India.

2. The Committee first took up the issue about the trial of HPV vaccine on the children in Khammam district of Andhra Pradesh and Vadodra district of Gujarat and reported deaths of the children therefrom in its meeting held on 06th April, 2010 during the course of examination of Demands for Grants (2010-11) of Department of Health Research and sought exact status in this regard from the Secretary, Department of Health Research. Subsequently, taking serious view of the procedural and ethical lapses on the part of the Ministry, the Committee sought the matter of allowing trial of the vaccine as also the approval for its marketing in the country to be enquired into. The Committee also desired the Ministry to take further appropriate action in the matter and apprise it of the follow-up action taken in this regard at the earliest. As a sequel to the Committee's recommendation, a Committee was appointed by the Government of India to enquire into"Alleged Irregularities in the Conduct of Studies Using Human Papilloma Virus (HPV) Vaccine" by Programme for Appropriate Technology in Health (PATH) in India on 15th April,2010. The Final Report of the Committee appointed by the Government of India to enquire into"Alleged Irregularities in the Conduct of Studies Using Human Papilloma Virus (HPV) Vaccine" by Programme for Appropriate Technology in Health(PATH) in India was made on 15th February,2011.

3. The Committee thereafter deliberated on the subject in its meetings held on 25th July, 2011 and 24th May, 2013.

4. During the course of examination of the subject, the Committee heard the views of the Secretary, Department of Health Research and other officials of the Department on 25th July,2011 and Secretary, Department of Health Research and Drug Controller General of India(DCGI) on 24th May, 2013.

5. During the finalization of its Report, the Committee relied upon the following documents/papers:-

(i) Background note received from the Ministry;

(ii) Final Report of the Committee Appointed by the Government of India to enquire into"Alleged Irregularities in the Conduct of Studies Using Human Papilloma Virus (HPV) Vaccine" by Programme for Appropriate Technology in Health(PATH) in India;

(iii) Oral Evidences tendered by Secretary, Department of Health Research and DCGI; and

(iv) Replies to the questionnaires received from the Department of Health Research.

6. The Committee considered the Draft Report and adopted the same in its meeting held on 29th August, 2013.

7. For facility of reference and convenience, observations and recommendations of the Committee have been printed in bold letters in the body of the Report.

NEW DELHI;
29th August, 2013
Bhadra7, 1935 (Saka)

Brajesh Pathak
Chairman,
Department-related Parliamentary
Standing Committee on Health and Family Welfare

ACRONYMS

1. AE- Adverse Event.
2. AEFI- Adverse Event Following Immunization.
3. ANM- Auxiliary Nurse Midwife.
4. AP- Andhra Pradesh.
5. AIIMS- All India Institute of Medical Sciences
6. CDSCO-Central Drugs Standard Control Organisation.
7. CTRI- Clinical Trials Registry- India.
8. CORT- Centre for operations Research and Training
9. DCGI- Drug Controller General of India.
10. DG, ICMR- Director General, Indian Council of Medical Research
11. FCRA-Foreign Currency Regulation Act
12. FERA- Foreign Exchange Regulation Act
13. FEMA- Foreign Exchange Management Act
14. GCP-Good Clinical Practice
15. GAVI- Global Alliance for Vaccines and Immunization
16. MEA-Ministry of External Affairs
17. MHA- Ministry of Home Affairs
18. HPV- Human Papilloma Virus.
19. HMSC- Health Ministry Screening Committee
20. ICMR- Indian Council of Medical Research.
21. MoU- Memorandum of Understanding.
22. MEA-Ministry of External Affairs
23. MHA- Ministry of Home Affairs
24. NGO- Non-Governmental Organization
25. NTAGI- National Technical Advisory Group on Immunization
26. O&G- Obstetrics and Gynaecology
27. PATH-Programme for Appropriate Technology in Health.
28. PBC-Public Benefit Corporation
29. ROC- Registrar of Companies
30. RBI- Reserve Bank of India
31. SAE- Serious Adverse Event.
32. UIP- Universal Immunization Programme.
33. USFDA-United States Food and Drug Administration

REPORT

I. BACKGROUND

1.1 During March, 2010 the entire world was shocked by the media reports about the deaths of some female children and adolescents in Khammam district of Andhra Pradesh after being administered Human Papilloma Virus (HPV) vaccines. The vaccination trials were carried out by an American agency *viz.* Programme for Appropriate Technology in Health (PATH). The project was reportedly funded by Bill and Melinda Gates Foundation, an American charity.

1.2 Several questions were asked and concerns expressed in the media and well meaning quarters on the role of government agencies including Indian Council of Medical Research (ICMR) and Drugs Controller General of India (DCGI) in approving and facilitating the trials, which was against all laws of the land and even international ethical norms and rules; misuse of government funds, man-power, facilities and infrastructure for a private project of dubious nature; use of logo of National Rural Health Mission (NRHM), an official programme of the Union Government during these vaccination drives to give it respectability and official endorsement; and above all the blatant violation by PATH of all regulatory and ethical norms laid down by the Government of India for the purpose as also possible violations of such norms prescribed and very scrupulously enforced in the Country of its origin *viz.* United States of America.

1.3 Taking cognizance of these reports, the Committee (2009-10) which was examining the Demand for Grants (2010-11) of the Department of Health Research at that point of time sought a detailed clarification from the Government in the matter. In response the Secretary of the Department of Health Research and DG, ICMR informed the Committee that it was a vaccine against the Human Papilloma Virus which causes cervical cancer in women. The Drugs Controller General, India had given approval for marketing of HPV vaccines in India as a vaccine to be prescribed by the clinicians as per schedule 'Y' of the Drugs and Cosmetics Rules and then for a post-marketing surveillance trial. The Committee was informed that the proposal for trial came two years earlier (though later on during the

Committee's examination it was proved that it began in 2006) before the ICMR through PATH, an American agency, and the logic for allowing the trial was to see acceptability of this vaccine on Indian population. Besides, these trials were approved by the National Ethical Committee and the State Ethical Committee.

1.4 Attention of the Secretary was drawn to DCGI guidelines wherein Phase III trials cannot be conducted on children until a similar trial was conducted on adults. It was admitted by the Secretary that the DCGI guidelines were not adhered to in the present case but this vaccine is given before the sexual activity begins and then it protects against cancer. That was the reason for allowing trials on girls of the age of 10-14 years. The Committee was assured that State Governments of Andhra Pradesh and Gujarat would be asked to get the ongoing clinical trial stopped immediately.

1.5 Hugely perturbed by these blatant violations, the Committee in its Forty first Report on Demands for Grants (2010-11) of the Department of Health Research made the following recommendations on this issue:

> "Taking serious view of procedural and ethical lapses on the part of the Ministry, the Committee sought the matter of allowing trial of the vaccine as also the approval for its marketing in the country to be enquired into by a premier investigating agency and to take further appropriate follow-up action in the matter. It also asked that findings of the investigating agency and the follow-up action taken in this regard may be furnished to the Committee at the earliest. The Committee, taking a serious view in the matter, recommends to the Department of Health Research that in future all guidelines and norms should be adhered to before allowing trials of any drug including vaccines on Indian population. The Committee also recommends that the DCGI should observe optimum precautions and follow all norms and guidelines while allowing marketing of any drug including the vaccines in the Indian market".

1.6 The Department of Health Research in its Action Taken Note on the above recommendations submitted the following:

"PATH in partnership with State Governments of Gujarat and Andhra Pradesh was implementing an operational research study related to cancer of cervix prevention in India. ICMR is providing technical support & consultation for development of protocol and plan of monitoring.

The study utilized both the brands of HPV vaccines available in the market (Gardasil by Merck in Andhra Pradesh; and Cervarix by GSK in Gujarat). In view of certain complaints received, the State Governments have been advised not to carry out further vaccination till further orders. To ascertain the facts of the matter, Minister for Health & Family Welfare appointed a Committee comprising of Dr. S.S. Agarwal, former Director, Advanced Centre for Training, Research, Education on Cancer, Dr. S.P. Aggarwal, former DGHS and Dr. Sunita Mittal, HoD, Obstetrics & Gynaecology, AIIMS to investigate ethical issues raised in the matter."

1.7 Not being satisfied with the action taken by the Government on its Recommendations, the Committee in its Forty eighth Report further recommended the following:

The Committee observes that as a result of its intervention, the State Governments have been advised by the Department not to carry out HPV vaccinations and a Committee has been appointed to investigate ethical issues raised in the matter. The Committee is not aware about the date of setting up of the Committee. However, the absence of any specific time-line for submission of Report of the Committee in the Action Taken Note given by the Department makes the Committee somewhat apprehensive. Like so many Committees set up by the Government, findings of this Committee, as and when received, may remain on paper only. The Committee, therefore, recommends that every effort should be made to expedite the Report of this Committee so that real facts about the HPV Vaccine trial are made known without any further delay and corrective measures not only in respect of this case but for all such ongoing/proposed clinical trials of drugs/vaccines are taken. The Committee also recommends that the Department should at least now work in close coordination with other concerned departments/organizations to undertake a comprehensive

analysis of the process of granting permission to research studies having hazardous effects on health and put in place a fool-proof system for pre-empting unethical research studies.

1.8 Considering the enormity of the wrong doing/criminality involved, and the dilly-dallying attitude of the Government in taking exemplary corrective action, the Committee took it up for detailed examination. The succeeding paragraphs contain the details of the matter, Committee's findings and recommendations.

1.9 Cancer of the cervix (mouth of uterus) popularly called Cervical Cancer has been there ever since the dawn of human race. Over the years, preventive and treatment protocols have been developed by medical experts.

1.10 The Committee was given to understand that on June 1, 2006 the American drug regulator, the U. S. Food and Drug Administration (USFDA) approved the first vaccine to prevent HPV virus that is claimed to cause 70% of cervical cancers, under the brand name of Gardasil by a US drug company namely, Merck.

1.11 In the very same month, an American organization called Program for Appropriate Technology in Health (PATH) embarked upon a large scale, 5-year long (June 2006 to May 2011) project with "the main objective …..to generate and disseminate evidence for informed public sector introduction of HPV vaccines" in four countries, India, Uganda, Peru and Vietnam. Interestingly these four countries have different ethnic populations: India (Indo-Aryans, Dravidians, Tribals etc.), Uganda (Negroid), Peru (Hispanics) and Vietnam (Mongoloids). The Committee has been given to understand that ethnicity is relevant in the determination of safety and efficacy of some drugs. What would be of further interest, as per World Health Organization (WHO) is that all these countries have state-funded national vaccine immunization programs, which if expanded to include Gardasil, would mean tremendous financial benefit to the then sole manufacturer.

1.12 With this background a clinical trial under the title 'Post-licensure observational study of Human Papilloma Virus Vaccination – Demonstration Project' was undertaken by Programme for Appropriate Technology in Health (PATH), an

agency of American origin. The Indian Council of Medical Research (ICMR), which is the highest body in the Country for medical research and related matters lent its platform to PATH in an improper and unlawful manner. The State Governments of Andhra Pradesh and Gujarat swayed by the involvement of ICMR followed suit.

II. NATURE OF PROJECT

2.1 Given the controversy surrounding the project, the Committee was keen to know from the Government the exact nature of the project. The Committee noticed that there was fundamental difference between the perceptions of Drugs Controller General of India (DCGI) and Department of Health Research (DHR) / Indian Council of Medical Research (ICMR) on the actual nature of the project. The DCGI was of the opinion that since human subjects, as part of the research, were receiving invasive intervention like vaccines, the clinical trial rules must be enforced. Experts also upheld these views and were very clear about it. However, PATH described the project as an "observational study" since "it did not conform to the definition of clinical trial".

2.2 The Committee found from the information furnished to it that ICMR representative on the Project Advisory Committee not only opposed DCGI but also argued that the nature of the project does not require them to follow the clinical trial rules, including reporting of serious adverse effects within a specific time frame.

2.3 The Committee in this regard took note of the expert opinion given in the Inquiry Committee report which questioned the PATH description of the project and observed that since "the demonstration project is a study of a pharmaceutical product carried out on humans and since the primary objectives include the study of serious adverse effects, it is clear that clinical trial rules and guidelines should apply".

2.4 In fact, the Inquiry Committee in one of its findings very pointedly stated that the investigators had variously labeled the research project carried out by them as

"Observational Study/Demonstrational Study," etc. to establish that the study was not a clinical trial. But, since the project had been carried as research on human participants, it had to follow all the guidelines and statutory requirements applicable for research on human participants.

2.5 The Committee finds the entire matter very intriguing and fishy. The choice of countries and population groups; the monopolistic nature, at that point of time, of the product being pushed; the unlimited market potential and opportunities in the universal immunization progammes of the respective countries are all pointers to a well planned scheme to commercially exploit a situation. Had PATH been successful in getting the HPV vaccine included in the universal immunization programme of the concerned countries, this would have generated windfall profit for the manufacturer(s) by way of automatic sale, year after year, without any promotional or marketing expenses. It is well known that once introduced into the immunization programme it becomes politically impossible to stop any vaccination. To achieve this end effortlessly without going through the arduous and strictly regulated route of clinical trials, PATH resorted to an element of subterfuge by calling the clinical trials as "Observational Studies" or "Demonstration Project" and various such expressions. Thus, the interest, safety and well being of subjects were completely jeopardized by PATH by using self-determined and self-servicing nomenclature which is not only highly deplorable but a serious breach of law of the land. The Committee is not aware about the strategy followed by PATH in the remaining three countries *viz.* Uganda, Vietnam and Peru. The Government should take up the matter with the Governments of these countries through diplomatic channels to know the truth of the matter and take appropriate necessary action, accordingly. The Committee would also like to be apprised of the responses of these countries in the matter.

III. ROLE OF DEPARTMENT OF HEALTH RESEARCH/INDIAN COUNCIL OF MEDICAL RESEARCH

3.1 One of the functions mandated to the Department of Health Research/ICMR is promotion and coordination of basic, applied, clinical and operational research in medical, health and bio-medical field through development of infrastructure, manpower and skills. Uniform Ethical Guidelines for bio-medical Research on human subjects are incorporated in Good Clinical Practice (GCP) and ICMR documents. These guidelines outline the procedure for Ethics Committees review of clinical trials in India using the human beings as participants. All institutions and investigators in the country which carry out any form of biomedical research involving human beings are obliged to follow these guidelines in letter and spirit to protect participants.

3.2 As per the records made available to the Committee, the first documented contact made by PATH with ICMR took place, as early as, on 5th October 2006. An employee of PATH India sent an e-mail to Deputy Director of National AIDS Research Institute, ICMR expressing sorrow that she could not travel to Seattle, United States for "Formative Research Workshop" (on HPV vaccine) scheduled for October 24-26, 2006. Apparently, PATH functionaries were in touch with ICMR officials on an informal basis in the past.

3.3 Within a few days, a meeting took place between PATH and ICMR officials on 13 October, 2006 at PATH office in New Delhi where it was stated that "HPV vaccine, when available (in India), can prevent HPV and cervical cancer." The possibility of Global Alliance for Vaccines and Immunizations (GAVI) subsidizing the cost of vaccine for the first 2 - 4 years was also mentioned. Evidence (on role, utility of vaccine) made available to Government of India and States would "help to decide on public sector (state funded) introduction of the vaccine."

3.4 On 16 November, 2006, a draft Memorandum of Understanding (MoU) between PATH and ICMR was circulated by PATH which stated that "Parties (PATH and ICMR) desiring to explore collaboration to support public sector decision regarding HPV vaccine introduction in India and… to generate necessary evidence to

allow…..the possible introduction of HPV vaccine into India's Universal Immunization Programme."

3.5 Thus as early as October-November 2006, it was clear that the main objective of PATH project was to generate evidence that would facilitate the introduction of HPV vaccine Gardasil into government-funded immunization program in India. This appears to be a promotional activity for the benefit of manufacturing company because at that time only one HPV vaccine, Gardasil had been approved abroad, though not in India. Indeed "the key object of the project activities in India is to gather information and help the government make a decision about the introduction of HPV vaccine". The Country Director of PATH in India emphasized that "this needs to be our consistent message throughout the project."

In the formal proposal submitted by PATH to the ICMR on Project Proposals involving Foreign Collaboration/Assistance, the applicant clearly stated under Para 9. Objectives of the Project: "…….Introduction of HPV vaccines into Universal Immunization Program." The Committee found repeated mention of similar objectives at several places in various documents submitted by the Ministry. The Memorandum of Understanding (MoU) was signed by PATH and ICMR on 20 February, 2007. At that time only Gardasil was marketed in some countries in the world though not approved for use in India. The MoU stated that the purpose of the project was:

(i) Increasing understanding of HPV vaccine (i.e. Gardasil) introduction.
(ii) To help in decision-making related to the use of HPV (i.e. Gardasil) vaccine in the public and private sector.

3.6 The Committee enquired from the Secretary of Department of Health Research (DHR) and DG, ICMR, as to whether the Department or CDSCO, before approving the project had really reviewed its actual design. The Committee highlighted the observations of the experts of the Inquiry Committee who have opined that the design of the project itself was faulty. For instance, in the documents there was no column whatsoever for

Serious Adverse Events (SAE) and no diary was to be maintained as part of the protocol.

3.7 Moreover, much before the trials started, many expected side effects including anaphylaxis (severe allergic reaction), syncope, convulsions, asthma, central demyelinating diseases, acute disseminated encephalomyelitis, Idiopathic Thrombopenia Purpura, etc. were known. And astonishingly, as the records stated, while ICMR functionary was worried of bad publicity in case of side effects, PATH did not provide for urgent expert medical attention in case of serious adverse events whether known or unexpected.

3.8 After going through the final report and interactions with the Secretaries of the Department of Health and Family Welfare and the Department of Health Research/ICMR and DCGI, the Committee felt that it needs clarification as to under what category, permission was given to PATH to conduct such study on the Indian people and whether the programme was a clinical trial or promotional activity. The Committee took note of the fact that the Enquiry Committee meeting held on September 27, 2010, noted as under (Appendix 20.5):

> "....Besides the factual information about the terms of reference the Committee was greatly concerned with the aspect of commercial interests of manufacturers influencing the Government policy on this expensive vaccine. The committee observed that the study was initiated by PATH on its own …….. without any reference from the National Technical Advisory Group on Immunization (NTAGI), the official body of the GOI on vaccines.....It is not clear whether the State expenses were funded by PATH or came from their own resources. The monetary contributions of ICMR are also not clear. The Committee therefore felt that it would be in the fitness of the inquiry to document the sources and magnitude of funding of the study".

3.9 In this connection, the Committee also noted that one of the roles assigned to ICMR in the MOU signed by the Director General of the ICMR was "advising on plans for results dissemination to support decision making for use of the HPV vaccine".

3.10 **The Committee is unable to understand as to how ICMR could commit itself to support "the use of the HPV vaccine" in an MOU signed in the year 2007 even before the vaccine was approved for use in the country, which actually happened in 2008. The Committee also questions the decision of ICMR to commit itself to promote the drug for inclusion in the Universal Immunization Programme (UIP) even before any independent study about its utility and rationale of inclusion in UIP was undertaken.**

3.11 The Committee noted that there were many gaps and missing links in the whole episode and enquired as to when ICMR came into contact with PATH. First a vaccine should get the approval from the Government and then only it can be used in UIP. Secretary, Department of Health Research/DG, ICMR while responding to the queries, informed that the first discussion with the PATH was held in 2006 followed by signing of agreement in the year 2007. At that time HPV vaccine had not been approved in India and no study was conducted on it. This was all a preparatory exercise.

3.12 The Committee was informed that the trial was on the two vaccines approved by DCGI. It was also stated that these vaccines had been tested abroad and on a limited number of people in India as per rules following which DCGI had given the approval for their marketing in the country, and then a post-marketing surveillance trial.

3.13 The Committee in this connection took note of the fact that before any drug is tested especially on a large population of 25,000- 32,000 children between the age of 10 to 14, then according to the CDSCO guidelines, no such trial can be conducted on children until a similar, prior trial is conducted on adults to determine efficacy and safety.

3.14 The Secretary, Department of Health Research/DG, ICMR while deposing before the Committee in its meeting held on 25th July, 2011, stated that the terms of reference of the Enquiry Committee was to find out any relation between the deaths with the administration of vaccine and any incidents of irregularities in the implementation of the study. He stated that the Enquiry Committee concluded that the deaths reported during trial had no uniform pattern to link them to the administration of vaccines.

3.15 The Committee noted that all the seven deaths were summarily dismissed as unrelated to vaccinations without in-depth investigations. According to Inquiry Committee report, the speculative causes were suicides, accidental drowning in well (why not suicide?), muyalaria, viral infections, sub-arachnoid haemorrhage (without autopsy) etc. The Committee has been given to understand that suicidal ideation is caused by many drugs. Since then one more death due to suicide in case of Gardasil has been reported in addition to 5 deaths reported during 2009-10. Therefore, HPV vaccine as a possible, if not probable, cause of suicidal ideation cannot be ruled out.

3.16 The Secretary of DHR/ DG, ICMR acknowledged that certain irregularities were reported in the implementation of the project. With regard to Informed Consent, he said that though the consent was taken properly in Gujarat, there were gross violations of norms in Andhra Pradesh. He informed the Committee that DCGI, had sought explanation for the incidents of irregularities.

3.17 The Committee took note of Secretary's comments but sought to know as to how ethical it was on the part of ICMR to become a party to a project in the name of Public-Private Partnership (PPP mode). How ICMR, which is mandated to formulate ethical guidelines for researchers, can become a direct party in such a study. The Secretary, Department of Health Research admitted that presence of ICMR in the Project's Advisory Committee-responsible and accountable for various acts of omissions and commissions-clearly indicates Conflict of Interest. Therefore, ICMR owes full moral responsibility for numerous irregularities reportedly committed in the study.

3.18 The Committee feels that there was serious dereliction of duty by many of the Institutions and individuals involved. The Committee observes that ICMR representatives, instead of ensuring highest levels of ethical standards in research studies, apparently acted at the behest of the PATH in promoting the interests of manufacturers of the HPV Vaccine.

3.19 It was unwise on the part of ICMR to go in the PPP mode with PATH, as such an involvement gives rise to grave Conflict of Interest. The Committee takes a serious view of the role of ICMR in the entire episode and is constrained to observe that ICMR should have been more responsible in the matter. The Committee strongly recommends that the Ministry may review the activities of ICMR functionaries involved in PATH project.

3.20 Secretary of Department of Health Research and DG, ICMR in their defense also claimed that the ICMR had fulfilled the written role entrusted to it but the irregularities that took place during the implementation of the study clearly indicate that there were certain micro (ground) level issues requiring more attention. For instance, it was noticed that States were not even capable of monitoring the adverse effects. He stated that this all was a learning exercise.

3.21 It maybe pertinent to mention here that the safety, efficacy and introduction of vaccines in India is handled by National Technical Advisory Group on Immunization (NTAGI). Thus, at the very outset, ICMR should have either referred PATH to NTAGI or at least taken NTAGI on board.

3.22 The Committee from its examination has found that DHR/ICMR have completely failed to perform their mandated role and responsibility as the apex body for medical research in the Country. Rather, in their over-enthusiasm to act as a willing facilitator to the machinations of PATH

they have even transgressed into the domain of other bodies/agencies which deserves the strongest condemnation and strictest action against them. The Committee fails to understand as to why ICMR took so much interest and initiative in this project when the safety, efficacy and introduction of vaccines in India is handled by National Technical Advisory Group on Immunization (NTAGI). The submissions of the Secretary, DHR/DG, ICMR before the Committee about the commencement of the project, facts of the case and the action taken have also failed to stand scrutiny during the Committee's examination of the matter. The Committee, therefore, reiterates the recommendation made in their Forty-first Report that the matter of allowing trial of the vaccine as also the approval for its marketing in the Country be inquired into by a premier investigating agency and appropriate action be taken thereafter by the Government in the matter. The Committee expects the Government not to procrastinate in this matter any further.

IV. ROLE OF DRUGS CONTROLLER GENERAL, INDIA (DCGI)

4.1 The Committee noted that as per Rule122-DA and Schedule Y of the Drugs and Cosmetics Rules, 1945 made under the Drugs and Cosmetics Act, 1940, no clinical trial on a drug can be conducted except under, and in accordance with the permission in writing, of the Licensing Authority i.e. DCGI. All vaccines are deemed to be drugs. Clinical trials of pharmaceutical products are conducted on human subjects in the country to determine or verify safety and/or efficacy. Every permission for conducting clinical trials also, inter alia, includes a condition that in event of trial related injury or death, the sponsor will provide complete medical care as well as compensation. Statement to this effect needs to be incorporated in the Informed Consent Form. The details of compensation provided are to be intimated to the office of DCGI.

4.2 The Committee noted from the evidence available that the nature of the PATH project made it Post-marketing Phase IV Clinical Trial under Drugs and Cosmetic Rules. It was on this basis that DCGI approved the clinical trial on 22 April, 2009 and had earlier issued import licenses on 23 December, 2008 though it was incorrect on the part of DCGI to issue import licences on Form 11 under Rule 33 which states:

Import of drugs for examination, test or analysis: Small quantities of drugs the import of which is otherwise prohibited under section 10 of the Act may be imported for the purpose of examination, test or analysis subject to the following conditions:

(a) No drug shall be imported for such purpose except under a licence in Form 11;

(b) the licensee shall use the substances imported under the license exclusively for purposes of examination, test or analysis and shall carry on such examination, test or analysis in the place specified in the license, or in such other places as the licensing authority may from time to time authorize.

4.3 Since both Gardasil and Cervarix had received marketing approval from CDSCO on 4 July, 2008 and 10 September, 2008 respectively, DCGI should have issued Import Licenses on Form 10 which is applicable to import of drugs already approved.

4.4 The so called Demonstration Project of PATH has the objectives as follows:

Primary Outcomes:

- Number & percentage of vaccinated girls.
- Number & percentage of vaccinated girls experiencing Serious Adverse Events (SAEs)
- Number & percentage of vaccinated girls experiencing non-Serious Adverse Events.
- Timeliness of reporting SAEs to local, state and national authorities.
- Timeliness of reporting Non-SAEs to local, state and national authorities.

4.5 Thus it is clear that PATH project had two well defined and specific objectives:

(a) The commercial objective of the project was to generate evidence, data and arguments to support inclusion of HPV vaccines into India's state-funded Universal Immunization Program (UIP), and

(b) The scientific purpose was to collect data on serious and non-serious adverse effects. Given that similar projects were launched in Peru, Uganda and Vietnam, the entire exercise would have collected side effect profiles of HPV vaccines in all the ethnic groups that reside in developing countries. Such data would be invaluable to promote the two branded, patented, single source HPV vaccines as safe all over the world.

4.6 The Committee's examination has proved that DCGI has also played a very questionable role in the entire matter. Initially, it took a call that since human subjects, as part of the studies, were receiving invasive intervention like immunization, clinical trial rules must be enforced. However, it remained as a silent spectator thereafter, even when its own rules and regulations were being so fragrantly violated. The approvals of clinical trials, marketing approval and import licenses by DCGI appear to be irregular. Therefore, the role of DCGI in this entire matter should also be inquired into.

V. MARKETING APPROVAL TO HPV VACCINES IN INDIA

5.1 Before approving any new drug (including new vaccines), under Drugs and Cosmetics Rules, it is mandatory to conduct Phase III clinical trials in India to determine any ethnic differences in the safety and efficacy profiles. As per records made available to the Committee the following clinical trials, albeit, under various names, were conducted:

Gardasil (Merck): Clinical trials were conducted on 108 subjects (girls in the age group of 9-15 years). Several violations took place in the trial: (a) trials should have been conducted in adults first before exposing children to known and unknown side effects, (b) in adolescents and children the trials should

have been conducted from "top to bottom" age groups i.e. first in adolescents (13-15 years) followed by children (9-12 years). This was not done. Vaccines were administered to children irrespective of age at the same time.

Cervarix (GSK): Clinical trials were conducted on 162 subjects (adults in the age group of 18-35 years). Yet permission was given to use the vaccine in children (10-14 years) in violation of rules.

VI. INQUIRY COMMITTEE

(a) Composition and Terms of Reference

6.1 The Committee was informed that because of the concerns raised at different fora, the study was suspended and an Enquiry Committee was constituted by the Govt. of India vide notification No. V.25011/160/2010-HR dated 15th April, 2010, to enquire into "Alleged irregularities" in the conduct of studies using Human Papilloma Virus (HPV) vaccines by PATH in India.

The inquiry committee consisted of the following:

(1) Dr. S.S. Agarwal, former Director, Advanced Centre for Training, Research, Education on Cancer,

(2) Dr. S.P. Aggarwal, former DGHS, and

(3) Dr. Sunita Mittal, HoD, Obstetrics & Gynaecology, AIIMS

6.2 The terms of reference of the Committee were to enquire into:

(i) Link between the deaths and vaccine, if any, and

(ii) Ethical Issues of subjecting children of marginalized populations to these studies, and investigations in children without appropriate Consent.

6.3 The Committee was assisted by the following experts:

(i) Dr. Rani Kumar, Dean, AIIMS

(ii) Dr. A. K. Dutta, Head of Pediatrics, Kalawati Saran Hospital

(iii) Dr. Y. K. Gupta, Head of Pharmacology, AIIMS

(b) <u>Conflict of Interest</u>

6.4 The Committee sought information from the Ministry of Health and Family Welfare (MoHFW) as to whether members of the Inquiry Committee were asked to file Conflict of Interest declarations. In response the Ministry replied: "No written Conflict of Interest declarations were sought from the core members of the Inquiry Committee as well as experts. It was understood that if there is any conflict, highly learned members will point it out."

6.5 In order to verify the Ministry's claim, the Committee picked just one member i.e., Professor and HoD of the Department of Obstetrics and Gynaecology (O&G) of All India Institute of Medical Sciences (AIIMS). It was found that manufacturers of Gardasil, Merck was sponsoring and funding a trial in the Department of O&G at AIIMS to determine if 2 doses of Gardasil can be used safely and effectively instead of 3 doses. Documents received by the Committee in connection with the examination of AIIMS also revealed that the individual in question availed the hospitality of these very sponsors during the said individual's visit to Seoul to attend a conference. The FCRA application form was, therefore, deliberately left incomplete to hide this truth. All these speaks of a serious conflict of interest of this member of the Inquiry Committee.

6.6 The Committee also found that the Ministry appointed a senior official of ICMR (described as Resource Person) to assist the Inquiry Committee. The concerned individual was the main link between ICMR and PATH, and had participated actively in all discussions, meetings and helped PATH to carry out the project proactively in every respect right from the beginning in October 2006. As such he had a clear Conflict of Interest and could not be relied upon to give correct information and unbiased opinion. Indeed he should have been summoned as a witness to answer questions and not as an official Resource Person attached to the Enquiry Committee.

(c) Adverse Events Reporting

6.7 The Committee examined the final Report of the Inquiry Committee constituted to enquire into the alleged irregularities in the conduct of studies using HPV vaccines by PATH in India. In its first meeting held on 21-4-2010, the Inquiry Committee sought details on the following core issues:

1. When did PATH approach ICMR for trial runs?
2. With whose permission was MOU signed?
3. Did President of ICMR approve?
4. Whether it had approval of the Screening Committee?
5. Approval of DCGI.
6. Details of reimbursements provided so far by PATH to ICMR
7. Names of beneficiaries.
8. Expenditure incurred by ICMR so far on all items including travel expenses.

6.8 However in its second meeting on 30 April, 2010, no discussion took place on the above crucial issues since the Inquiry Committee wished "to restrict itself to the terms of reference."

6.9 Inexplicably, however, as the records placed before the Committee proved, this decision did not prevent the Inquiry Committee from going into and recommending actions on other matters far beyond the terms of reference.

6.10 The Committee notes that once this matter was taken up by it, the Government appointed an Inquiry Committee on 15 April, 2010 to inquire into 'alleged irregularities in the conduct of the studies using HPV vaccines by PATH in India'. The Committee has noted the serious conflict of interest of members of this Inquiry Committee with the subject matter. The Committee, therefore, strongly deprecates the Government for appointing a committee to inquire into such a serious matter in such a casual manner even without ascertaining as to whether any of the members of the said Inquiry Committee were having any conflict of interest with the subject matter of inquiry.

6.11 The Committee finds it very intriguing as to when the Inquiry Committee after having sought details of some core issues in the very first meeting of the Committee on 21 April, 2007 subsequently chose not to pursue them purportedly because 'it wanted to restrict itself to its terms of reference'. These core issues raised by the Inquiry Committee earlier, if pursued to their logical end, would not only have provided the Inquiry Committee a lot more clarity in unraveling the truth but also the Country would have known the exact details as to what transpired in this sordid incident.

(d) Informed Consent

6.12 Obtaining Informed Consent from study subjects is a core requirement in the conduct of clinical trials and protection of human rights. In case of minors, the Consent has to be signed by parents/guardians. In the case of uneducated signatories, an independent person has to explain and witness the consent process. The Informed Consent document approved by various Ethics Committees on PATH project included the sentence: "I have read the information in this consent form (or it has been read to me). I consent to allow my daughter to receive three doses of HPV vaccines." In the case of Andhra Pradesh 9,543 forms were signed, 1,948 had thumb impressions while hostel warden had signed 2,763 forms. In the case of Gujarat 6,217 forms were signed, 3,944 had thumb impressions and 545 were either signed or carried thumb impression of guardians. The data shows that a very large number of parents/guardians were illiterate and could not even sign in their local language i.e. Telugu or Gujarati.

6.13 One of the experts, while going into the question of Informed consent in great detail, in two reports, has pointed out glaring discrepancies. Out of 100 consent forms for AP Project taken for study, it was found that signatures of witnesses were missing in 69 forms. In many forms there were no dates while in others the signature of just one person appeared in seven forms

The legality of the Andhra Pradesh State Government circular directing all Headmasters/Wardens in all private/government/ashram schools to sign the consent forms on behalf of parents/guardians was also questionable.

6.14 The Inquiry Committee, while going through the above report, noticed the following irregularities and discrepancies in the study:

(i) The warden/teachers/headmasters were not given written permission by the parents/guardians to sign on behalf of their girls.

(ii) On many forms witness had not signed and of the forms which are signed, it is not clear whether they are signed by full time government employees, as per rules.

(iii) Neither the photograph nor the photo ID card of parents/guardians/wardens is pasted in consent form.

(iv) On many forms investigator has not signed.

(v) On some forms signature of parents/guardians is not matching with their names.

(vi) The date of vaccination is much earlier than the date of signature of parents/guardian in the consent forms. Apparently they were obtained post-facto.

(vii) In some forms, the name is of the father but signature is of probably mother (lady's name).

6.15 Secretary, DHR and DG, ICMR while deposing before the Committee, reiterated that the regulatory approvals given to the project were in proper order and due attention was paid to the guidelines and formats for seeking consent. However, during the implementation of the project certain irregularities took place. He admitted there were cases of discrepancies in A.P. He admitted that many consent forms were filled up by the Principal on behalf of the students. He admitted to gross violation in the recording of SAEs also. He informed the Committee that keeping all these observations in view the DCGI, besides issuing immediate instructions to stop the study, had sought explanations for irregularities committed during the study.

6.16 The Committee observes that obtaining informed consent from study subjects is a fundamental requirement in the conduct of clinical trials to ensure that the human rights of the study subjects are ensured.

In case of minors it is mandatory that the consent be signed by parents/guardians. For the uneducated subjects, the law requires an independent person to explain and witness the consent process. The Committee is however, deeply shocked to find that in Andhra Pradesh out of the 9543 forms, 1948 forms have thumb impressions while hostel wardens have signed 2763 forms. In Gujarat, out of the 6217 forms 3944 have thumb impressions and 5454 either signed or carried thumb impressions of guardians. The data also revealed that a very large number of parents/guardians are illiterate and could not even write in their local languages viz. Telugu or Gujarati. The Committee is further shocked to find from one of the reports that out of 100 consent forms for Andhra Pradesh project signatures of witnesses were missing in 69 forms. In many forms there were no dates. One particular person had signed seven forms. In fact the legality of Andhra Pradesh State Government directing headmasters in all private/Government/ashram/schools to sign the consent form on behalf of parents/guardians is highly questionable. The absence of photographs of parents/guardians/wardens on consent forms, the absence of signatures of investigators; the signatures of parents/guardians not matching with their names; the date of vaccination being much earlier than the date of signature of parents/guardian in the consent forms, etc. all speak of grave irregularities.

6.17 The Committee, accordingly, concludes that most, if not all consent forms, were carelessly filled-up and were incomplete and inaccurate. The full explanation, role, usefulness and pros and cons of vaccination had not been properly communicated to the parents/guardians. The Committee observes that there is a gross violation of the concept and legal requirement of consent which had been substantiated by the experts. The Committee takes a serious view of the violations and strongly recommends that on the basis of the above facts, PATH should be made accountable and the Ministry should take appropriate action in the matter including taking legal action against it for breach of various laws of the land and possible violations of laws of the Country of its origin.

6.18 The Committee was informed that the basic aim of the study was to evaluate strategies for introduction and delivery of the vaccines in the public sector. Strangely four of the five primary outcome measures proposed in the study related to evaluation and determination of safety of the vaccines.

6.19 One of the experts has stated that there was lack of rigour in the design regarding reporting and dealing with serious adverse events. He has pointed out absence of preparedness in the event of any such occurrence that would put children at grave risk. The side effects mentioned by the manufacturers themselves were revised several times and now include serious health issues. Since there were contra-indications to the use of the vaccines, the reasons for not ascertaining contra-indications before the girls were vaccinated is clearly an act of willful negligence.. The design of the project neither took the possibility of Serious Adverse Event (SAE) seriously nor was there any attention paid to the need for an independent monitoring agency. Consequently action on investigations into the causes of deaths took an unacceptably long time. A number of discrepancies and gaps in the investigations of the deaths have also been pointed out. There was no diary card based reporting of adverse events for recording minor or major adverse events in the study protocol in such a large study. This resulted in gross under reporting of the adverse events.

6.20 Another expert, while analyzing deaths and Adverse Events Following Immunizations (AEFI) has observed after reviewing all seven deaths (five deaths from AP in the Gardasil group and two deaths in Gujarat from Cervarix group), that there was no common pattern to the deaths that would suggest that these were caused by the vaccine. However, the reporting system as per Government of India surveillance of vaccine preventable disease guidelines notification was not done within time limit in two cases in AP and both the cases in Gujarat. There was no uniformity in the reporting system of AEFI in both the States. The primary end point of the study was to find out the number of girls having serious and non serious adverse events following vaccination through routine UIP system. He has opined that in

this regard first of all routine system of reporting should have been verified in both States.

6.21 Another expert has stated that the reporting of non-serious AEs was grossly under reported and hence the accuracy of SAEs is doubtful as well. It has been observed that delay in reporting and investigations of deaths could have been due to sole dependence on routine UIP protocol. It was a significant lapse in the protocol and execution of the study. While reporting on safety aspects in the study, it has been pointed out that there was absence of preparedness to handle Serious Adverse Events (SAE) like anaphylaxis, cardiac arrest, seizures, etc. occurring at the sites of vaccine administration. Though such serious adverse events might be rare but it was advisable to be well prepared for such an eventuality through adequate training of health workers. Assessment of the immune status of the participants by the ANM, ASHA or the health workers was virtually non-existent. These issues needed to be addressed as prescribing information of the HPV vaccines specifically contra-indicates administration in immune-compromised subjects (such as HIV/AIDS etc.).

6.22 The Committee, in the light of the observations made by experts, feels that the methodology and implementation of the study at both the places was full of flaws. The Committee is of the view that since the population under study was vulnerable, utmost caution should have been exercised in the implementation of the study. The Committee also recommends that there should be an independent monitoring mechanism in such a study involving human participants so that the accurate recording of AEs and SAEs could be made. The findings of the experts clearly indicate that the safety and rights of the children in this vaccination project were highly compromised and violated. The Committee is also concerned over the fact that there was no insurance cover for the children. The Committee strongly recommends that while allowing any such trial in future, all the lapses pointed out by the experts should be addressed effectively. ICMR and DCGI should ensure strict adherence to the guidelines, methodology and monitoring.

(e) Role of Ethics Committees

6.23 While examining the role of the Ethics Committees in both the States, one of the experts pointed out that Ethics Committees were supposed to meet periodically to evaluate and monitor the progress of the project and review SAE reports. No such meetings were held by the Committees. Only after reports of deaths appeared in the media, the meetings of these Committees were held.

6.24 The Committee takes a serious note of the fact that both the Ethics Committees existed only as a formality and they did not play the role they were designated for. This is a clear dereliction of duty on the part of the Ethics Committees. The Committee apart from recommending suitable action in the matter, strongly recommends that there should be a mechanism in place to take appropriate action against such dereliction of duty on the part of the Ethics Committees. There should be specific guidelines for Ethics Committees and the Ethics Committees should strictly follow them. The functioning of Ethics Committees should be regularly monitored.

(f) Use of Official Machinery

6.25 The Committee has noted that the information/publicity material displayed/distributed at trial sites implied that the Government had started a vaccination programme. Thus, the credibility of the Universal Immunization Programme (UIP) was used to promote private, foreign interests. It has been found that the funds meant for the NRHM were used, without authorization for monitoring and transportation of the vaccines to the fields for use in the project.

6.26 **The Committee observes that the wrongful use of the NRHM logo for a project implemented by a private, foreign agency as well as the identification of this project with the UIP has adversely affected**

and damaged the credibility of the programme as well as that of the NRHM. The Committee, therefore, recommends that such practices of diverting public funds for advancing interests of a private agency should never be allowed in future. The Committee strongly recommends that strict action should be taken against those officials responsible for such lapses.

6.27 Besides, the Committee notes that no information had been provided to Indian authorities about funding of the project except that it was reportedly funded by Bill and Melinda Gates Foundation and that the vaccines had been donated by the manufacturers. The information regarding financial investments of ICMR and State Governments in the project was not provided, though the States clearly provided cold chain and manpower for immunization. **The Committee, accordingly, observes that it might have been more prudent if the National Technical Advisory group on Immunization (NTAGI) had been brought into the picture right in the beginning to review and give its views on the study prior to its approval and implementation.**

6.28 No information is available on the total outlay on the project spent by PATH, ICMR, state governments of Andhra Pradesh and Gujarat (immunization staff, cold chain system, equipment, transportation etc.). According to the documents submitted by PATH to ICMR/Health Ministry Screening Committee, the total outlay by PATH for expenses in India was Rs. 29,76,000. However Centre for Operations Research and Training (CORT), a sub-contractor of PATH had quoted US$ 83,889 (first year) and US$ 96,472 (second year), which is not included in the figure submitted to ICMR/HMSC.

6.29 Considering the above lapses and irregularities committed by PATH during the course of conducting the trials on hapless tribal children in Andhra Pradesh and Gujarat, the Committee is convinced that the authorities concerned did not exercise due diligence in scrutinizing the publicity material of PATH. Blurring the distinction between the UIP and PATH project due to the involvement of the

State Governments in the project and ignoring the financial contribution of ICMR and the State Governments are very serious issues. The Committee, therefore, recommends that the Ministry should investigate into the above acts of omissions and commissions and take necessary action against those who are found responsible for breach of rules and regulations.

(g) Action taken on the Inquiry Committee Report

6.30 With a view to find out the action taken by the Government on the findings of the Inquiry Committee, the Committee again heard the Secretary, Department of Health Research/DG, ICMR along with DCGI at its meeting held on 24th May, 2013. The Secretary informed the Committee that after the submission of Report by the Inquiry Committee, they were formally called to give explanation in the year 2011. In addition, clarifications were also sought from them in between which were formally answered to. The Committee in the said meeting desired to know whether criminal inquiry, if any, has been initiated against PATH on account of the following irregularities in the conduct of trial as pointed out by the Inquiry Committee:

(i) Irregularities in obtaining consent forms and actual implementation of the consent process;

(ii) Lack of monitoring and preparedness to deal with serious adverse events;

(iii) Inclusion of vulnerable and tribal population groups;

(iv) Blurring of distinction between Universal Immunization Programme and PATH study;

(v) Absence of insurance coverage for the study participants; and

(vi) Inclusion of the statement in the consent form that "you will not be charged for your daughter to receive the vaccine" that could be construed as covert inducement.

6.31 The Committee also sought to know as to whether any compensation was awarded to the families of children for suppression of material information before administering vaccines.

6.32 The Committee also took note of the Action Taken Note submitted by Department of Health Research wherein it was informed that subsequent to findings of the Inquiry Committee following action was taken:

(i) PATH was informed about suggestions made by the Committee;

(ii) Principal Investigators of other suspended studies on HPV vaccines were informed to get their studies re-examined from respective Ethics Committees after addressing the concerns raised by the Inquiry Committee;

(iii) DCG(I) was informed of the suggestions of the Committee for necessary action; and

(iv) Suggestions were forwarded to the relevant authority for inclusion in the Draft bill on Biomedical Research on Human Subjects.

6.33 DCG(I) informed the Committee that subsequent to findings of the Inquiry Committee; the following action was taken:

(i) Both the manufacturers of HPV vaccines have been asked to submit additional data for 4 years on PSURs (Periodic Safety Update Reports), every 6 months for first 2 years, and annually during the subsequent 2 years, and to submit protocol for approval for conducting post marketing surveillance study;

(ii) Proposal to amend the definition of "New Drug" under rule 122-E would be taken up for consideration; and,

(iii) In future the following steps would be ensured before approving a clinical trial by DCG(I): (a) every clinical trial is to be registered at ICMR's clinical trial registry of India; (b) every approval would include a condition for provision of complete medical care in case of study related injury/death & the statement to this effect is to be included in the informed consent: (c) DCG(I) should be informed about death/ injury: (d) Schedule 'Y' would be amended to expand the responsibilities of sponsors, investigators & Ethics Committees; and (e) the consent forms are to be amended to

include details of address and occupations of subject giving socio-economic background.

6.34 The Committee is amazed at the audacity of DCGI to merely repeat various steps which it proposes to take as if they are new, additional measures. All these are already part of the written rules and are supposed to be followed by all sponsors. Except for slight amendment in the Informed Consent Form, there is nothing new in the ATN submitted by DCGI.

6.35 The Committee observes that the Department has nothing fresh to offer in the status note as the same information was furnished by it in December, 2012 vide its updated note on Action Taken after availability of Report of nquiry Committee.

6.36 **The Committee not being convinced with the action taken by the Department or DCGI, feels that the whole issue has been diluted and no accountability has been fixed on the erring Officials/Departments for the gross violations committed in the conduct of Study. The Committee also feels that a very casual approach has been taken by the Department in the matter and their replies lack any concrete action to protect and safeguard the health of our people.**

6.37 **The Committee also noticed lack of firm action on the part of DCGI, to avoid such irregularities in future. One of the actions proposed by the DCGI to check any recurrence of such gross violations was 'proposal to amend the definition of New Drug during the next meeting'. The same assurance was given by DCGI in December, 2012. The Committee, accordingly, observes that response of the Department and DCGI is very casual, bureaucratic and lacks any sense of urgency. The Committee feels that DCGI is not very serious in bringing improvements in the system. It, therefore, desires the Ministry to ensure compliance by DCGI.**

VII. PROGRAMME FOR APPROPRIATE TECHNOLOGY IN HEALTH (PATH)

7.1 The Committee during the course of its present examination sought information from the Government about PATH in order have a better understanding of its legal status and its *locus standi* in carrying out various activities on the Indian soil including the project in question where apparently several laws of India and possibly of its country of origin had been violated.

7.2 The information furnished to the Committee reveals that PATH describes itself as an "International nonprofit, non-government organization based in the United States." Legally, it is a Public Benefit Corporation (PBC) registered (number 600588751 dated 28th August 1981) by the Corporation and Charities Division in the State of Washington. For all practical purposes its legal status in US is equivalent to a Registered Society in the Indian context. It is certainly not a commercial company and hence would not be subject to the jurisdiction of Company Law Board or Registrar of Companies in India. Incidentally, Ford Foundation is also a PBC (Registration number 768093 dated 15th January 1936). Under American laws organizations such as Trusts, Fraternal Societies, Savings & Loan Associations, Municipal Utility Services etc. are all registered as PBCs.

7.3 Under Indian rules, foreign non-commercial organizations such as PATH wanting to set up an office in India are required to obtain (a) permission from the Ministry of External Affairs (MEA) from "political angle" (**annexure A**) and (b) permission from Ministry of Home Affairs (MHA) from "security angle" (**Annexure B**). In the latter case, application needs to be forwarded through proper channel such as Ministry of Health & Family Welfare for health-related activities, Ministry of Human Resources for education related activities, Ministry of Labour for trade union or workers related activities etc. Once such an approval is accorded, then an office can be setup which should naturally abide by all other laws of the land such as income tax, shop & establishment act, municipal and other applicable laws, just to mention a few.

7.4 The Committee asked the Department to direct PATH to provide details of various mandatory permissions required by foreign agencies, including charities, for and in connection with opening office in India and the date of opening of its office in

India. Unbelievably, the exact date of opening the office is not even known to its functionaries in New Delhi. To begin with vide its letter dated 5-3-2012, PATH claimed that "it has a Liaison Office status under Income Tax Rules." Since no such provision exists, after prolonged correspondence it settled for 19th April 1999 as the date of opening office based on the fact that its PAN card (number AAFCP2249G) is dated 19th April 1999. The Committee was intrigued because PAN card is issued just for income tax purposes and nothing else. Income Tax Department does not go about permitting foreign entities to open offices in India. In any case PAN card is not a replacement for Ministry of External Affairs and Ministry of Home Affairs approvals. Besides, the application for issuance of PAN card must have been made much before 19th April 1999 there being no online system of obtaining PAN card instantaneously. It can be safely assumed that the date of opening office has to be much earlier than 19th April 1999.

7.5 PATH also produced copy of a letter dated 16-3-1999 from PATH office in US to the Exchange Control Department of the Reserve Bank of India along with reply dated 19-4-1999 received by PATH in US on 29-4-1999. It merely stated that since PATH is "not engaged in any commercial, trading or industrial activity," it does not need "RBI permission from foreign exchange angle. *However you may seek necessary approval from the Government of India or other statutory/regulatory bodies as applicable."* Apparently PATH paid no attention to RBI's sane advice. Even before the letter reached PATH office in the United States on 29-4-1999, it had already opened its office in India.

7.6 The Foreign Exchange Regulation Act (FERA) was replaced with Foreign Exchange Management Act (FEMA) on 1-6-2000. PATH produced post-facto permission from the Reserve Bank of India dated 25-5-2009 which clearly stated:

> *"RBI permission (is) granted from the foreign exchange angle….and should not be construed to convey the approval of any other statutory authority or Government under any other laws/regulations."* Moreover, the Liaison Office is permitted to undertake "solely liaison work for the head office" as mentioned below:
>
> 1. Representing in India the parent company/group companies

2. Promoting export, import from/to India.
3. Promoting technical/financial collaborations between parent/group companies and companies in India.
4. Acting as a communication channel between the parent company and Indian companies.

"The office in India will not render any consultancy or any other services directly/indirectly with or without any consideration."

In addition *"Permission granted by RBI is limited to and for the purpose of the provisions of FEMA-2000 and shall not be construed in any way as regularizing, condoning or in any manner validating any irregularities, contraventions and other lapses, if any, under the provisions of any other law."*

7.7 It is clear that the back dated permission obtained after 10 years of having opened its office in India was merely and exclusively from foreign exchange angle and not a substitute for approval from MEA and MHA.

7.8 Finally and belatedly PATH produced a certificate from the Registrar of Companies (RoC) dated 23-9-2009 stating that PATH, a company originally incorporated in US, had filed documents on 10-09-2009 notifying establishment of place of business in India w.e.f 19-4-1999. The Certificate was apparently issued in violation of its own rules that states that documents must be submitted within 30 days of the establishment of "place of business." In any case such a certificate cannot and does not obviate the need to obtain baseline, mandatory permission from MEA and MHA. Moreover RoC deals with commercial companies, not foreign trusts, foundations and charities.

7.9 PATH also claimed that it had received "permission" from the Ministry of Health and Family Welfare to set up an office in India. The post-facto letter dated 27-4-2001 (two years after PATH admits having opened the office in India) is not a permission at all but a vague, non-specific statement to say that PATH was "engaged in health care related activities".

7.10 According to the published Annual Report of PATH for the year 2008, it received funding in "excess of US $ 1,000" from many governmental sources including the Ministry of Health & Family Welfare, Government of India. However, in response to Rajya Sabha Question Number 952 on 3-8-2010, the Health Minister denied any Ministry funding to PATH.

7.11 The Committee is concerned that if PATH can set up an office in India so easily without getting the required mandatory approvals/permissions, then individuals and entities inimical to the interest of the country can do the same. The Committee expresses its concern that paper and shell companies can be easily registered in many jurisdictions and then set up a place of business in India as "Liaison offices" with no questions being asked. It is surprising that security and intelligence agencies did not raise an eyebrow on the way a foreign entity entered India virtually incognito through the backdoor. The Committee desires that such incidents should not be allowed in future. The Government should tighten the rules lest one day foreign citizens, with deep roots in organizations/nations inimical to India, set up offices in the country to engage in anti-national and/or unlawful activities.

7.12 It is apparent the PATH has exploited with impunity the loopholes in our system as also the absence of a nodal point or a single window for maintaining a data bank of foreign entities entering the Country for setting up their offices. Given the multiplicity of agencies involved in processing such requests there is a definite need for a nodal agency which would keep a tab on all such existing and aspiring agencies from the point of view of having obtained all necessary clearances/permissions before commencing their operations in India. The Committee strongly recommends that government set up one such umbrella agency which should be linked to all the agencies that are involved in processing such requests. The Committee desires that within three months such an agency should be put in place and start functioning. The proposed nodal agency should be a part of MHA with a well established coordination mechanism with the MEA so that undeserving cases are dealt forthwith through

diplomatic channels. All ministries/departments/agencies/state governments/other entities should be required to share details of all requests/proposals from foreign entities for setting up offices in any form with this nodal agency.

7.13 Coming to the instant case, it is established that PATH by carrying out the clinical trials for HPV vaccines in Andhra Pradesh and Gujarat under the pretext of observation/demonstration project has violated all laws and regulations laid down for clinical trials by the Government. While doing so, its sole aim has been to promote the commercial interests of HPV vaccine manufacturers who would have reaped windfall profits had PATH been successful in getting the HPV vaccine included in the UIP of the Country. This is a serious breach of trust by any entity as the project involved life and safety of girl children and adolescents who were mostly unaware of the implications of vaccination. The violation is also a serious breach of medical ethics. This act of PATH is a clear cut violation of the human rights of these girl children and adolescents. It also deems it an established case of child abuse. The Committee, therefore, recommends action by the Government against PATH. The Committee also desires that the National Human Rights Commission and National Commission for Protection of Children Rights may take up this matter from the point of view of the violation of human rights and child abuse. The National Commission for Women should also *suo motu* take cognizance of this case as all the poor and hapless subjects are females.

7.14 The Ministry of Health and Family Welfare should without wasting time report the violations indulged in by PATH to international bodies like WHO and UNICEF so as to ensure that appropriate remedial action is initiated by these agencies worldwide.

7.15 The Committee also desires that the Ministry of Health and Family Welfare may take up the matter through the Ministry of External Affairs with the US Government so as to ensure that appropriate action is taken

against PATH under the laws of its Country of origin in case of any violations of laws there.

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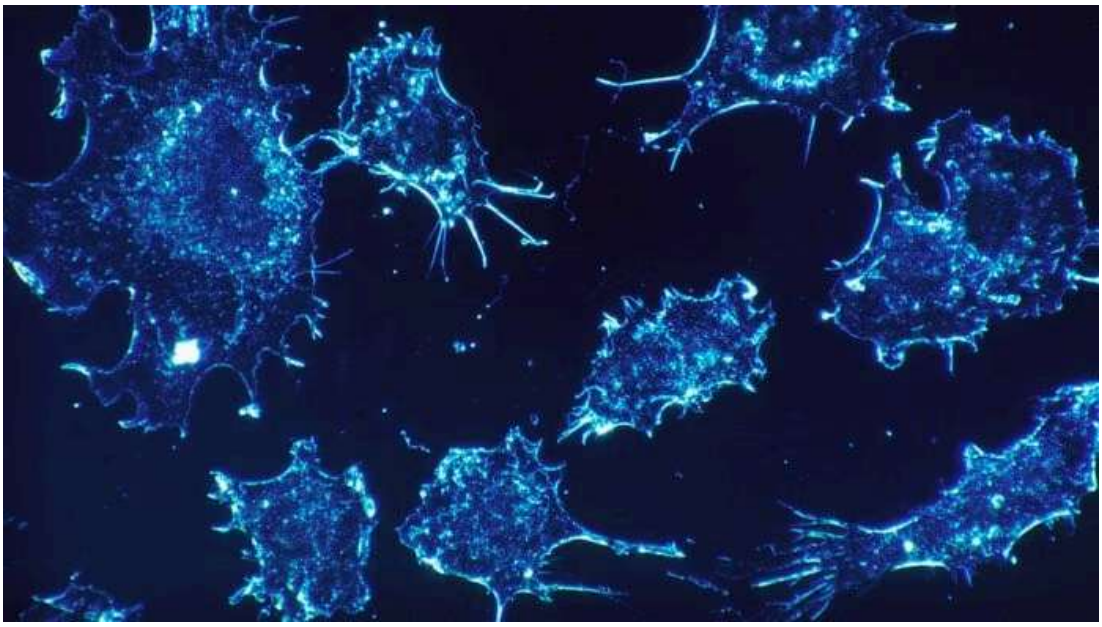
ThePrint

ANNEXURE P/4

Health

Delhi, 1st state to launch HPV vaccine for cervical cancer, sees numbers fall. Blame pandemic

ABHISHEK DEY 28 January, 2022 10:56 am IST



Cancer cells | Representational image | Pixabay

New Delhi: The Human Papilloma Virus (HPV) vaccination drive in Delhi, which is aimed at preventing cervical cancer among young women, has been one of the casualties of regular classes in schools being suspended for the Covid-19 pandemic, said senior government officials.

The officials said they haven't been able to collate data on HPV vaccination since April 2020, largely because of the focus on Covid-19 management. When it is done, the numbers would be very low, they said.

They said that around 13,000 girls aged between 11 and 13 years — mostly in batches from schools — were administered HPV vaccines free of cost in Delhi between November 2016 and March 2020.

Delhi became the first state in the country in November 2016 to launch HPV vaccination as a public health programme. In 2017 and 2018, Punjab and Sikkim, too launched their own programmes.

Not only has closed schools hit the HPV vaccination drive hard, its roll-out across the country — The Union government is yet to include HPV vaccination in the universal immunisation programme (UIP) — is fiercely opposed by the Rashtriya Swayamsevak Sangh (RSS) and its affiliate, the Swadeshi Jagran Manch (SJM), who highlight the vaccine's potential adverse effects and question its utility.

India has a high caseload of cervical cancer, and it ranks second among all cancers in Indian women, after breast cancer. And HPV is believed to be associated with more than 80 per cent cervical cancer cases.

As part of the government programme, girls aged between 11-13 years are eligible to be vaccinated free of cost at the Delhi State Cancer Institute, through its centres in east Delhi's Dilshad Garden and west Delhi's Janak Puri, said a government circular which ThePrint has seen.

The centres are currently functional, but the turnout has dropped, said senior government officials in Delhi.

During the nationwide lockdown during the first wave of the pandemic in March 2020, physical classes were suspended in schools across states. Between March 2020 and December 2021, regular classes in Delhi's schools were suspended for around 90 weeks. Currently, they are suspended again, due to the third wave of Covid-19.

Also read: *India lagging in cervical cancer prevention, needs more screening, vaccination, experts say*

Numbers picked up before pandemic

Between November 2016 and March 2017, around 1,200 girls were administered HPV vaccination under the government programme in Delhi. The number rose to 3,700 in the period between April 2017 and December 2018. Around 8,100 were vaccinated between January 2019 and March 2020, said senior government officials, citing government records.

"The vaccination drive was clearly picking up each year. Once the vaccine was introduced into the state's public health profile, a large number of agencies, including the state government, municipal bodies and non-governmental organisations joined hands in creating awareness. Most awareness programmes would take place in public schools," said a senior official in the Delhi government who did not wish to be identified.

The official further said, "But schools are closed now. So, the numbers have severely declined. We have not been able to summarise data for nearly two years now because a large part of the system is engaged in Covid-19 management. Records are maintained. We can summarise the data later. But we can tell you that the numbers are very low."

Another senior government official said, "The HPV vaccine centres are open, but the turnout is low. It is largely because we no longer see batches of students coming from schools in the city. People can personally come to these centres and get the vaccines for free. But such cases are rare. The centres now see people once in a while."

ThePrint reached to Delhi government spokespersons and the office of health minister Satyendar Jain through phone calls and text messages for comments on their plan to revive the HPV vaccination drive, if any. No response was received from them till the time of publishing this report.

Resistance against HPV vaccine

The HPV vaccine has been facing strong resistance from the Rashtriya Swayamsevak Sangh (RSS) ever since the Union government expressed plans in December 2015 to introduce it in the universal immunisation programme and asked the sub-committee of the technical advisory group to look at the incidence of cervical cancer in India and take a call on the vaccine at the earliest, senior officials said.

In December 2016, the Swadeshi Jagran Manch (SJM), a cultural-economic organisation and an RSS-affiliate, wrote to the prime minister, highlighting risks of the vaccine, potential adverse effects and questioning its utility. Acting on a complaint to the Prime Minister's Office (PMO) by the SJM, the health ministry asked the drugs regulator to look into the matter and take "necessary actions".

"We still have the same stand on the issue. The vaccine has major safety concerns," Ashwani Mahajan, national co-convener of the Swadeshi Jagran Manch, told ThePrint.

Controversy regarding the vaccine surfaced in India in 2009, when a clinical trial project anchored by a US-based NGO to give the HPV vaccine to 32,000 children in Andhra Pradesh and Gujarat ran into rough weather after some deaths were reported. The project had to be discontinued and was cited by activists as an instance of multinational companies exploiting the poor for their clinical trials.

But in its report published in 2011, a copy of which ThePrint has seen, the Union government, based on the findings of a committee it had set up, said that the deaths were unrelated to the HPV vaccination drive.

"Several developed countries have not introduced it in their national healthcare programmes. India should also not introduce this vaccine in its universal immunisation programme," said Mahajan.

Approval for inclusion in UIP awaited

According to records of the World Health Organization (WHO), over 100 countries across the world have fully or partially introduced HPV vaccines in their national healthcare schedules — they include the US, UK, Canada, Australia, South Africa, Brazil, Argentina, New Zealand, Spain, Portugal, France and Japan.

India is not one of them, according to records of the central government and the WHO.

In January 2018, the National Technical Advisory Group on Immunisation, the highest technical body on vaccination, gave its approval to the introduction of the cervical cancer vaccine in India's universal immunisation programme, subject to the outcome of a 2012 case in the Supreme Court regarding adequate clinical trials of the vaccine — which still remains pending.

"Health is a state subject in India. But as far as the question regarding the Union government adding or not adding the vaccine in the universal immunisation programme is concerned, there is a due process to be followed," said a senior central government official.

ThePrint has sought comments from the Union health ministry, too, through an email. They did not respond till the time of publishing this report.

Nearly 4,20,000 cervical cancer cases at any point of time

HPV is a group of more than 150 viruses that cause 'papilloma', or warts, in parts of the body, including the genital areas. It is primarily spread by skin-to-skin contact and is responsible for a number of diseases, including cancers, especially cancer of the cervix (the neck of the uterus).

Cervical cancer ranks second among all cancers in Indian women, after breast cancer. HPV is believed to be associated with more than 80 per cent cervical cancers.

According to government data, an estimated 1,23,907 new cervical cancer cases are detected annually in India. Every year, 77,348 deaths occur from it. At any given point of time, nearly 4,20,000 cervical cancer cases are present in the country.

(by Saikat Niyogi)

Also read: *India's cancer problem — not enough clinical trials and lack of access to those being done*

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ANNEXURE P/5

Health minister launches Human Papillomavirus vaccination vaccine campaign

TNN | Nov 9, 2017, 07.40 AM IST



MANSA: Punjab health and family welfare minister Brahm Mohindra on Wednesday commenced the Human Papillomavirus (HPV) vaccination campaign for nearly 10,000 girl students in Mansa. The minister was accompanied by principal secretary, health, Anjali Bhawra.

Mohindra said doctors had been directed to take care of every child while administering vaccination. He said the state government had allocated Rs 5 crore for free distribution of this vaccine for girl students in 450 government and 470 private schools of Bathinda and Mansa.

Mohindra said he wished that not even a single child suffered from cancer in the Malwa belt and that the 'Cancer Train' soon became history.

"We are quite concerned over the rising number of cancer cases and this is an initiative to keep our girl children healthy," he said. Expressing concern over the rising number of cervical cancer cases in the world, he said 2.5 lakh deaths were reported every year in the world and 67,000 deaths were from India alone.

He said he was aware of shortage of doctors in government hospitals and the government would deal this issue by introducing jobs for the practitioners with a monthly salary of at least Rs 40,000.

Further, he said a 5-member committee had been formed to investigate the reasons behind the rising instances of dengue in the state and it would submit its report within 15 days. He said a total of 11,132 cases of dengue had been reported in Punjab till date and 32 people have suspected to have died due to it.

ANNEXURE P/6

Centre urges States to create awareness and take steps for prevention of cervical cancer among girl students

प्रविष्टि तिथि: 22 DEC 2022 9:24AM by PIB Delhi

Key Highlights:

- *National Technical Advisory Group for Immunization (NTAGI) has recommended introduction of HPV Vaccine in the Universal Immunization Programme (UIP) with a one-time catch-up for 9-14 year-old adolescent girls followed with routine introduction at 9 years*
- *The vaccination would be provided primarily through schools (Grade based approach: 5th-l0th). In order to reach those girls who are unable to attend school on the campaign day, the vaccination would be provided at a health facility while for out-of-school girls the campaign would be conducted through Community Outreach and Mobile teams*

The Centre has written to all States and Union Territories to create awareness on prevention of cervical cancer and the importance of HPV vaccine among girl students across the country.

In a joint letter by the Union Education Secretary Shri Sanjay Kumar and Union Health Secretary Shri Rajesh Bhushan it has been highlighted that globally, cervical cancer is the 4th most common cancer in women. In India, cervical cancer is the second most common cancer in women and India contributes o the largest proportion of global cervical cancer burden. Cervical cancer is a preventable and curable disease, as long as it is detected early and manage deffectively. Most cervical cancers are associated with the Human Papilloma Virus(HPV)and the HPV vaccine can prevent most cases of cervical cancer if the vaccine is given before girls or women are exposed to the virus. Prevention through vaccination is one of the pillars of the Global Strategy adopted by WHO for the elimination of cervical cancer.

It is mentioned that the National Technical Advisory Group for Immunization (NTAGI) has recommended introduction of HPV Vaccine in the Universal Immunization Programme (UIP) with a one-time catch-up for 9-14 year-old adolescent girls followed with routine introduction at 9years.

The vaccination would be provided primarily through schools (Grade based approach: 5th-l0th) as school enrolment of girls is high. In order to reach those girls who are unable to attend school on the campaign day, the vaccination would be provided at a health facility while for out-of-school girls the campaign would be conducted through Community Outreach and Mobile teams based on age (9-14 years). For registration, recording and reporting of vaccination numbers, the U-WIN App would be used.

In the letter, the States/ UTs have been requested to issue necessary directions at appropriate levels for taking up the following activities in order to make the campaign a successful:

- Organizing HPV vaccination centres in schools for vaccination.
- Directing District Education Officer to support District Immunization Officer and be part of efforts of District Task Force on Immunization (DTFI) under District Magistrate.
- Coordinating with Government School & Private School Management Board in the district.
- Identifying a nodal person in each school to coordinate vaccination activities and collate the number of 9-14 years of girls in the school and bulk upload the same in U-WIN.
- Generating awareness through school teachers to all parents during Special Parents-Teachers' Meeting (PTAs).
- Supporting in generating an up-to date list of all types of school (UDISE+) in each block for micro planning and access to GlS mapping of schools to districts immunization officers for developing micro-plans so that none of the school is missed during the vaccination drive.
- Supporting health team to plan vaccination campaign in state excluding months of examination and holiday.

*****

NB/AK

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ANNEXURE P/7

MP News: Five Teenage Girls Hospitalised After HPV Vaccination In Gwalior

Five girls in Gwalior fell ill after receiving the HPV vaccine in Barkari Jigniya village. They reported vomiting, dizziness and fever and were admitted to Dabra Civil Hospital. Doctors said they are now stable. Families alleged they were not informed before vaccination. Health officials have ordered an inquiry into the incident during the state's cervical cancer vaccination drive.

FP News Service | **Updated:** Wednesday, March 11, 2026, 05:47 PM IST



MP News: Five Teenage Girls Hospitalised After HPV Vaccination In Gwalior | FP Photo

Gwalior (Madhya Pradesh): Five teenage girls fell ill after receiving the HPV vaccine in a village in Madhya Pradesh's Gwalior district, as reported on Wednesday. The incident was reported from Barkari Jigniya village in the Pichhor area of Dabra.

According to family members, the girls were taken for vaccination by an *anganwadi* worker without clearly informing their parents.

The families alleged that the girls were told they would receive ₹50k and assistance

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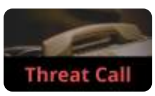
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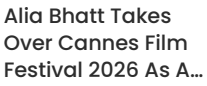
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for their marriage and were asked to sign a form before the vaccination.

After returning home, the girls informed their families about the vaccine. Soon after, they complained of vomiting, dizziness and fever, which worried their parents.

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The families then took them to the Civil Hospital in Dabra, where they were admitted for treatment.

Girls in stable condition

The girls - identified as Anjali, Poonam, Rajni, Bharti and Rekha from Barkari Jigniya village - were given primary medical care at the hospital. Doctors later said that all five girls are now stable and out of danger.

Family members alleged that they were not informed in advance about the vaccination and that their consent was not taken.

They claimed that health workers may have administered the vaccine to meet their vaccination targets.

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Responding to the incident, Chief Medical and Health Officer (CMHO) Dr Sachin Srivastava said the girls had complained of vomiting, fever and dizziness, but their condition is now normal.

He said a team has been formed to investigate the matter and the report is expected by the evening.

Officials also clarified that the HPV vaccine has been administered earlier as well. Previously it was available only through private purchase, but the government is now providing it free of cost.

The vaccination drive is part of the state government's campaign to protect teenage girls aged 14 - 15 years from cervical cancer.

The government aims to vaccinate around 8 lakh girls across the state through government hospitals and *anganwadi* centres.

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एचपीवी टीकाकरण के दौरान छात्राएं बेहोश

Apr 17, 2026 08:00 pm IST
Newswrap हिन्दुस्तान, बेगुसराय

Preferred

स्वास्थ्य विभाग ने की जांच, स्थिति सामान्य... स्वास्थ्य विभाग ने गंभीरता से लिया है। मामले की सूचना मिलते ही जिला प्रतिरक्षण अधिकारी डॉ. गोपाल मिश्रा, पीएचसी



बखरी, निज संवाददाता। प्रखंड के मध्य विद्यालय राटन में सर्वाइकल कैंसर से बचाव के लिए चल रहे एचपीवी टीकाकरण अभियान के दौरान दूसरी खुराक लेने के बाद कुछ छात्राओं के बेहोश होने की घटना को स्वास्थ्य विभाग ने गंभीरता से लिया है। मामले की सूचना मिलते ही जिला प्रतिरक्षण अधिकारी डॉ. गोपाल मिश्रा, पीएचसी के प्रभारी चिकित्सा अधिकारी डॉ. दीपक कुमार सहित स्वास्थ्य विभाग की टीम राटन गांव पहुंची और पूरे मामले की जांच-पड़ताल की। इसके बाद टीम ने प्रभावित छात्राओं के घर जाकर उनकी स्वास्थ्य स्थिति का भी जायजा लिया। इस दौरान अधिकारियों ने छात्राओं और उनके परिजनों को सर्वाइकल कैंसर तथा उससे बचाव के लिए चलाए जा रहे एचपीवी टीकाकरण अभियान के बारे में विस्तार से जानकारी दी।

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जरूर पढ़ें

पहले गेस पेपर की चर्चा, फिर गिरफ्तारी और अब पूरी NEET परीक्षा रद्द; कहां से शुरू हुआ 'पेपर लीक' का खेल?

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अगले 3 घंटों में यूपी में बारिश, ऑरेंज अलर्ट जारी, इन जिलों में दिन में छाया अंधेरा

तमिलनाडु में और मजबूत होगी विजय सरकार, AIADMK के एक धड़े ने भी किया समर्थन का ऐलान

विज्ञापन

ये भी पढ़ें: एचपीवी वैक्सीन पूरी तरह है सुरक्षित: सिविल सर्जन

उन्होंने स्पष्ट किया कि टीकाकरण पूरी तरह सुरक्षित है और घबराने की कोई आवश्यकता नहीं है। जानकारी के अनुसार, विद्यालय में एचपीवी टीकाकरण अभियान के तहत छात्राओं को दूसरी खुराक दी जा रही थी। इस दौरान तीन छात्राएं अचानक बेहोश हो गईं, जिससे कुछ देर के लिए विद्यालय परिसर में अफरा-तफरी का माहौल बन गया। हालांकि, बाद में सभी छात्राओं की स्थिति सामान्य बताई गई। मौके पर आयुष्मान आरोग्य मंदिर के चिकित्सक डॉ. अरुण कुमार ठाकुर, बीसीएम रतन कुमार सहित स्वास्थ्य विभाग के अन्य कर्मी उपस्थित थे।

लेखक के बारे में
Hindustan
हिन्दुस्तान भारत का प्रतिष्ठित समाचार पत्र है। इस पेज पर आप उन खबरों को पढ़ रहे हैं, जिनकी रिपोर्टिंग अखबार के रिपोर्टरों ने की है। ...और पढ़ें

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- आखिर यह कौन सा जीव है? लोगों ने बताया इच्छाधारी सांप, वैज्ञानिक भी हैरान
- CBSE 12वीं रिजल्ट को लेकर सोशल मीडिया पर हलचल, वायरल पोस्ट से टेंशन में छात्र

Schoolgirls faint during HPV vaccination

Apr 17, 2026 08:00 pm IST Newswrap Hindustan, Begusarai

The health department conducted an investigation, situation normal... the health department has taken it seriously.

Bakhri, Correspondent. The health department has taken seriously the incident of some students fainting after taking the second dose during the HPV vaccination campaign being run for the prevention of cervical cancer at Middle School Ratan of the block. Upon receiving information about the matter, District Immunization Officer Dr. Gopal Mishra, and the In-charge Medical Officer of the PHC, Dr. Deepak Kumar, along with a health department team, reached Ratan village and investigated the entire matter. After this, the team went to the homes of the affected students and also took stock of their health status. During this, officials gave detailed information to the students and their families about cervical cancer and the HPV vaccination campaign being run to prevent it.

They clarified that vaccination is completely safe and there is no need to panic. According to information, the second dose was being given to students under the HPV vaccination campaign in the school. During this, three students suddenly fainted, which created an atmosphere of chaos in the school premises for some time. However, later the condition of all the students was stated to be normal. On the occasion, Ayushman Arogya Mandir doctor Dr. Arun Kumar Thakur, BCM Ratan Kumar, and other health department personnel were present.

TRANSLATED COPY

ANNEXURE P/8

Regression of low-grade squamous intra-epithelial lesions in young women

Lancet 2004; 364: 1678–83

See Comment page 1642

Anna-Barbara Moscicki, Stephen Shiboski, Nancy K Hills, Kimberly J Powell, Naomi Jay, Evelyn N Hanson, Susanna Miller, Lisa K Canjura-Clayton, Sepidah Farhat, Jeanette M Broering, Teresa M Darragh

Departments of Pediatrics (A-B Moscicki MD, N K Hills MA, K J Powell NP, N Jay NP, E N Hanson NP, S Miller BA, L K Canjura-Clayton, S Farhat MS, J M Broering MPH), **Epidemiology and Biostatistics** (S Shiboski PhD), **and Anatomic Pathology** (T M Darragh MD), **University of California, San Francisco, CA, USA**

Correspondence to: Dr Anna-Barbara Moscicki, 3333 California Street, Suite 245 San Francisco, CA 94118, USA **annam@itsa.ucsf.edu**

Summary

Background **The aim of this study was to assess the probability of low-grade squamous intra-epithelial lesion (LSIL) regression in young women, and to examine the factors associated with this regression.**

Methods **In a longitudinal study of human papilloma virus (HPV) infection, female adolescents aged 13–22 years were examined every 4 months by cytology, colposcopy, and HPV DNA status. Both prevalent and incident LSIL cases were included in the analysis, with regression defined as at least three consecutive normal Pap smears.**

Findings **Median follow-up time from baseline (defined as the time of first LSIL diagnosis) for the 187 women with LSIL was 61 months (IQR 34–80). Median time they had been sexually active at diagnosis was 3·2 years (2·6–6·5). Probability of regression for the entire cohort was 61% (95% CI 53–70) at 12 months and 91% (84–99) at 36 months of follow-up. No associations were found between LSIL regression and HPV status at baseline, sexual behaviour, contraceptive use, substance or cigarette use, incident sexually transmitted infection, or biopsy. Multivariate analysis showed that only HPV status at the current visit was associated with rate of regression, whether infection was caused by one or more viral types (relative hazard=0·3 [95% CI 0·21–0·42], and 0·14 [0·08–0·25], respectively).**

Interpretation **The high rate of regression recorded in this study lends support to observation by cytology in the management of LSIL in female adolescents. Negative HPV status was associated with regression, suggesting that HPV testing could be helpful in monitoring LSIL.**

Introduction

Although human papillomavirus (HPV) infections are strongly linked to the development of cervical cancer, genital HPV infections are common in adolescent and young women, occurring in up to 70% of those who are sexually active.[1] More than 70% of HPV infections are transient.[1–3] A cytological manifestation of HPV, low-grade squamous intra-epithelial lesions (LSIL), is also quite common in women; about 25% of adolescent and young women develop LSIL after an HPV infection.[4] Although LSIL is thought to be a benign expression of HPV infection, risk factors for of development of LSIL seem to be distinct from those associated with acquiring HPV, which suggests that LSIL development is not a simple HPV infection.[4] Additionally, findings of observational studies in adult women have shown that about 20–40% of these lesions will progress to high-grade squamous intra-epithelial lesions (HSIL)—with only 50–60% spontaneously regressing.[5–7]

Most natural history studies of LSIL, however, have focused on women in their mid-20s to 40s who might represent a population with HPV infections that are already persistent.[5–10] We postulate that the rate of LSIL regression in adolescent and young women could be much higher than that reported for older women. The objective of this study was to define the probability of LSIL regression in adolescent and young women, and to examine the factors associated with this regression.

Methods

Participants

Women included in this analysis were part of a 10-year natural history study of HPV infection, which was initiated in 1990. The cohort population and study design have been described in detail elsewhere.[1] In brief, women aged 13–22 years who attended one of two family planning clinics between 1990 and 1994 were screened for cervical HPV DNA with a commercial test (HPV Profile, Digene Diagnostics, Silver Spring, MD, USA). Those who tested positive and were eligible—ie, with no previous history of squamous intra-epithelial lesion or treatment for such lesions—were asked to participate in the study. We also randomly recruited HPV-negative women as controls.[4]

Only women whose first cytological abnormality was LSIL (prevalent or incident) were judged to be eligible for analysis. We included both prevalent and incident cases to increase our overall sample size and because they are both indicative of common clinical scenarios. We regarded baseline to be the time of first LSIL. Median period of follow-up after this point was 61 months (IQR 34–80). Participants gave written consent according to guidelines approved by the Committee for Human Research, University of California, San Francisco.

Procedures

The protocols followed at every visit are described in detail elsewhere.[1] Median time between visits was

4 months (IQR 4–5). Every visit included cervical cytology, PCR testing for HPV DNA from cervical samples obtained with sterile Dacron swabs, and staff-administered questionnaires to obtain information on demographics, sexual behaviours, and substance use. Colposcopic examination of the vulva, vagina, cervix, and perianal areas was also undertaken for all patients, with 3% acetic acid.[1] Vaginal and cervical samples were obtained yearly or if the woman was symptomatic, to test for *Chlamydia trachomatis, Neisseria gonorrhoeae,* bacterial vaginosis,[11] and *Trichomonas vaginalis*.[12] An individual was regarded as positive for herpes simplex virus (HSV) if she tested positive with serology[13] at study entry or at any other visit, if a laboratory test for HSV yielded a positive result for an ulcer, or if she reported a history of HSV before a positive serology test or after a negative serology result. All cervical samples were tested with PCR as detailed previously.[1,4,14] Briefly, denatured biotin-labelled PCR product was hybridised to an array of immobilised oligonucleotides: HPV types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 55, 56, 58, 59, 68, MM4 (W13B), MM7 (P291), MM9 (P238A), 6, 11, 40, 42, 53, 54, 57, 66, MM8 (P155), and two β-globin controls to monitor consistency.[14] Additionally, we used an enhanced chemiluminescence system (ESL) in a dot blot format for the detection of biotinylated probes HPV 2, 67, 69, 70, and 72.

Two pathologists read all abnormal smears, and results were based on consensus. 10% of normal slides were also reviewed by standard University of California, San Francisco pathology quality assurance. At the start of the study, we used standard WHO cytological nomenclature for condyloma and cervical intra-epithelial neoplasia (CIN) 1–3. Women who were diagnosed with CIN 1–3 by cytology at any visit were asked to return for biopsy. We categorised diagnoses by the Bethesda system for rating cytology with the nomenclature LSIL and HSIL.[15]

To minimise possible misclassification bias due to the low sensitivity of a single Pap test, we defined regression as the first of three consecutive normal—ie, negative for atypical squamous cells of unknown significance, LSIL, and HSIL—Pap tests after diagnosis of LSIL. Women who had histologically confirmed HSIL were excluded from follow-up to receive treatment. These women were censored as persistent at that visit. Women who were subsequently diagnosed with HSIL by cytology but were shown to have lower grade disease by histology were judged to have persistent LSIL and continued to be followed up. Only first diagnosis of LSIL was included in the analysis.

Statistical analysis

Analyses were based on both incident and prevalent LSIL cases, with the primary outcome defined as the time between development and regression of LSIL. Initial comparisons of demographic characteristics between subgroups of woman were based on the Wilcoxon rank sum and Fisher's exact tests. Recordings of both the time of development and regression of LSIL were restricted to intervals between visits for women with incident outcomes, and time of development was limited to the interval between the time of first vaginal sexual intercourse and enrolment for prevalent cases. This method corresponds to double censoring of the outcome of interest. Estimates of the distribution of the time to LSIL regression were based on penalised maximum likelihood methods for interval censored event-time outcomes,[16] modified to allow double censoring.[17] These estimates were non-parametric and were constrained only by a specified degree of smoothness (selected via the Akaike information criterion) in the underlying hazard. They also allowed the effects of covariates to be investigated via proportional hazards assumption.[16]

We investigated factors associated with regression to normal cytology using proportional hazard regression models with both fixed and time-dependent covariates, including HPV status, years sexually active, age at diagnosis, number of variables related to sexual behaviour, smoking, substance use, contraceptive use, and cervical or vaginal infections. For women who were not available at all relevant follow-up times, time-dependent covariates were based on the closest preceding record. Models including time-dependent variables were fitted using parametric proportional hazard analysis for grouped survival data,[18] assuming that the time of development of LSIL coincided with the baseline visit. Hazards were modelled with parametric forms suggested by the penalised likelihood estimates, and estimated coefficients for fixed covariates were compared with results from analogous penalised likelihood models for consistency.

We also considered various alternate representations of HPV infection history in regression models. Because of the small number of individuals in all but the HPV 16 type specific groups, we grouped types into similar phylogenetic categories—eg, HPV 16-like type, HPV 18-like type, HPV 56-like type, and HPV other type (table 1). We created an additional category to account for simultaneous infections with multiple types. We did not group types by the conventional categorisations of high risk versus low risk, because of the small number of women (n=9 at baseline) with types in the low-risk category.

We also investigated the effect of current HPV status when adjusted for history of HPV (represented as a binary indicator of any HPV infection at baseline). We included current HPV infection as a three-level variable with categories for negative, positive for a single HPV type, or positive for two or more HPV types; single HPV-like types were collapsed since no differences were found in the single HPV 16-like types and the other single HPV infection groups.

Age (mean years, SD)	
At entry into study	19·7 (2·2)
At first LSIL diagnosis	20·8 (2·6)
Positive for HPV (any type) at LSIL diagnosis	149 (80%)
HPV 16 only	14 (7%)
HPV 16 and another type	31 (17%)
Single HPV 16-like type*	32 (17%)
Single HPV 18-like type†	18 (10%)
Single HPV 56-like type‡	7 (4%)
Uncategorised or consensus only§	26 (11%)
Multiple types	66 (35%)
Median follow-up, months (IQR)	61 (34–80)
Ethnic origin	
Non-Hispanic white	89 (47·8%)
African-American	21 (11·3%)
Hispanic	36 (19·4%)
Asian	23 (12·4%)
Mixed or other	17 (9·1%)
Socioeconomic status measured by mother's education level	
No college	91 (49·2%)
At least some college	94 (50·8%)
Number of sexual partners in lifetime at time of LSIL diagnosis, median (IQR)	7 (4-11)
Years sexually active at time of LSIL diagnosis median (IQR)	4·3 (2·6–6·5)
Chlamydia or gonorrhoea infection at time of LSIL diagnosis	14 (7·0 %)

Data are number (%) unless otherwise indicated. *Includes HPV types 16, 31, 33, 35, 52, 58, 67. †Includes HPV types 18, 26, 39, 45, 51, 59, 68, 69, 70. ‡Includes HPV types 53, 56, 66. §Includes all types not in any of the other groups (HPV types 6, 11, 40, 42, 54, 55, 57, 73, 82, 83, 84).

Table 1: **Demographic characteristics (n=187)**

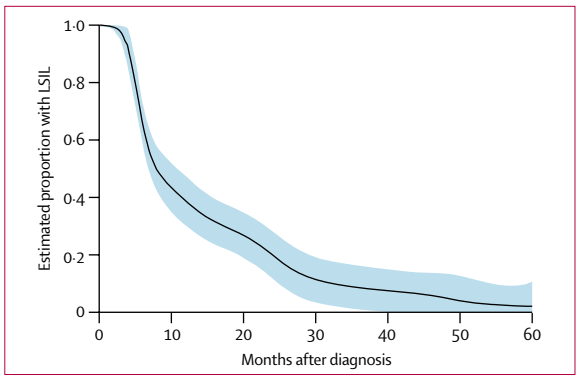


Figure: **Penalised likelihood estimate of time to LSIL regression**
Shaded region represents pointwise 95% CIs.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

899 women in our study of the natural history of HPV infection had valid cytology results; of these, 260 were diagnosed with LSIL by cytology at baseline or at a subsequent visit. 17 women were removed from the study because they had HSIL on histology, six left during the first year of the study because the protocol during 1990–91 called for women with histologically confirmed LSIL to be removed from the study for treatment (this protocol was amended to allow follow-up in 1991), 24 dropped out of their own accord immediately after LSIL diagnosis, and 20 remained in the study but had an insufficient number of follow-up visits to be included in the analysis. We also excluded six women who had missing covariate data, leaving 187 individuals eligible for study (table 1).

There were no significant differences in race, socioeconomic status, lifetime number of partners, years sexually active, age at time of diagnosis, or history of sexually transmitted infections between women excluded at the time of diagnosis and those included in the study. The excluded group was, however, significantly younger than the included group at study entry (mean 18·8 years [SD 2·0] *vs* 19·7 [2·2], p=0·01), and had a significantly higher rate of sexual partners per year of sexual activity than those who remained in the study (median 1·6 [IQR 1·1–2·8] *vs* 0·6 [0·3–0·9], p=0·0001).

Of the 187 women diagnosed with LSIL who were eligible for inclusion in this analysis, 55 (29%) had LSIL at baseline, whereas 132 (71%) developed LSIL during the course of the study. Median time to the first of three negative Pap tests for the overall cohort was 8 months (95% CI 7–11), and the probability of LSIL regression was 61% (53–0·70) at 12 months and 91% (84–99) at 36 months' follow-up (figure). The probability of progression to HSIL (n=6) within the same time period was 3% (0·7–6·0). The probability of regression within the following year for women whose cytology was still abnormal at 12 months was 51% (39–62), and the probability of regression for women whose cytology was still abnormal at 24 months was 60% (39–81).

To test for potential differences in our results due to under-representation of women who would go untreated if they were not referred for biopsy after their initial cytological diagnosis of LSIL, we did analyses in which the 17 cases of HSIL identified at biopsy were included by the assumption that they would have been identified to have HSIL by the Pap test (and thus be referred for biopsy) within 1–3 years. The probability of regression was not significantly different.

Inclusion of an indicator of prevalent LSIL as a covariate in the models described earlier showed that women with prevalent infection were significantly less likely to regress than those with incident cases (relative hazard=0·22 [95% CI 0·13–0·38]). This difference suggests that women diagnosed at entry into the study included both those who had recently developed LSIL and those who had acquired HPV some time ago and had persistent LSIL at entry, and is consistent with our results, which show that up to 10% of women could have LSIL for up to 3 years after diagnosis.

We used additional proportional hazards models to examine possible differences between women with conflicting biopsy results after cytological diagnosis. 67 of the 187 women with LSIL had biopsies, of which

30 were then confirmed as LSIL and 37 were histologically normal (median 1·2 months between Pap diagnosis and biopsy [IQR 0·9–1·9]). However, we noted no significant difference in time to regression between those who had LSIL confirmed by histology compared with those with a normal biopsy (relative hazard 0·82 [95% CI 0·59–1·15]). To examine the effect of biopsy on time to regression, we compared rates of regression in women who underwent biopsy and women who did not; no significant difference was recorded (0·62 [0·34–1·11]).

Because of the high number of condyloma diagnoses, we used similar tests to examine possible differences in time to regression for these women. No significant difference was noted for women diagnosed with cytological condyloma compared with cytological CIN 1 (0·87 [0·63–1·21]). Similarly, no differences were recorded in time to regression by age group (<21 years *vs* ⩾21 years; results not shown).

In preliminary analyses, the only baseline predictor variables associated with the outcome were presence of HPV 16-like only (relative hazard 0·61 [95% CI 0·39–0·96]) and the binary indicator of infection with two or more types of HPV at the time of diagnosis (0·62 [0·40–0·97]). Of the time-dependent covariates, current binary HPV status was strongly associated with LSIL regression (0·24 [0·18–0·34]), indicating reduced risk for regression in women with a recent positive HPV test. None of the behavioural or biological factors thought to be associated with LSIL regression were shown to be significantly linked, except for years sexually active at diagnosis (p=0·06) and vulvar warts (p=0·11). Estimates of regression coefficients for baseline covariates from penalised likelihood models were closely similar to those obtained in parametric regression models. Consequently, the latter were used in subsequent analysis.

Single HPV-type infection from any of the subgroups—HPV 16-like only (relative hazard 0·26 [95% CI 0·17–0·41]); HPV 18-like only (0·38 [0·20–0·73]); HPV 56-like only (0·15 [0·04–0·62]); and other (0·37 [0·22–0·63])—and infection with two or more HPV types (0·14 [0·08—0·25]) were all significantly associated with LSIL regression compared with no HPV in time dependent analysis. The HPV subgroups did not significantly differ in predicting LSIL regression. We did an additional analysis to assess whether a multiple-type infection truly reduced the relative hazard for LSIL regression. Since 60% of the multiple-type infections included HPV 16, we compared multiple-type infection with HPV 16 infection alone. Risks of LSIL regression associated with infection with multiple HPV types not including HPV 16 (0·39 [0·16–0·98]), and with multiple types including HPV 16 (0·37 [0·13–1·07]), were significantly different from infection with HPV 16 alone in time dependent analysis.

Our multivariate model—which included various measures of HPV infection status (at baseline and time-dependent) adjusted for age, years sexually active at the time of diagnosis, and vulvar warts—showed that overall HPV status at baseline was not significant in the preliminary analysis. When we controlled for history of vulvar warts, number of years sexually active, and age at diagnosis, current HPV status remained significant whether infection was single or multiple type (table 2). Adjustment for baseline HPV status did not affect the association between regression and current HPV status. Similarly, controlling for an indicator of prevalent LSIL at baseline (both as a single factor and as an interaction with other variables) and recruitment site did not affect the estimates shown in table 2.

HPV status*	Relative hazard (95% CI)
Negative for any type†	1·00
Positive for a single HPV type	0·3 (0·21–0·42)
Positive for multiple (⩾2) HPV types	0·14 (0·08–0·25)

*HPV status variable modelled as time dependent covariate. Analysis adjusted for age, years sexually active, and HPV status at diagnosis, and vulvar warts as time-dependent covariate. †Reference category.

Table 2: **Final model for HPV status as a time-dependent covariate in regression of cervical LSIL (n=187)**

Discussion

Our findings suggest that strategy of colposcopy for all adolescent and young women with LSIL is unwarranted and leads to unnecessary intervention, morbidity, and cost. Instead, assessment with serial cytology might be appropriate. In our study, LSIL spontaneously regressed in most women by 3 years of follow-up, showing the benign nature of this condition in adolescent and young women. This high rate of regression and low rate of progression is in accord with overall low rates of HSIL diagnosed by cytology or biopsy in this age group.[19] Our findings lend support to monitoring of adolescent and young women with LSIL diagnosed by cytology, and to the current option to delay referral until patients have had a second abnormal Pap smear 6 or 12 months after their first.[8] We noted additional benefit when follow-up was continued for another 1–2 years. Schlecht and colleagues[20] made similar recommendations for adult women on the basis of their findings that 88% of LSIL cases showed regression and that the mean time for progression from LSIL to HSIL was 85·7 months. However, our results should be interpreted with caution since our study was based on three cytology results per year, restricting its comparison to current clinical practice. Studies are needed to define appropriate screening strategies.

The substantial reductions in regression rates reported in adult women (40–60%) in many studies[5–7] are probably based on several factors. First, HPV infections in adolescents are extremely frequent and transient.[1] Since LSIL are clinical manifestations of HPV, the high rate of LSIL recorded in adolescents is not surprising.

The heightened rate of LSIL regression noted in young women indicates a high rate of resolution in HPV infections.[1] Older women with LSIL on cytology might represent a population with HPV infections that are not transient, but rather show true persistence, which is a risk for HSIL. Second, the low sensitivity of cytology for diagnosis of HSIL has been well documented. Most individuals with biopsy-confirmed HSIL are women referred for LSIL or atypical squamous cells of unknown significance. Because rates of HSIL are higher in older women than in younger women, the chance of misclassification for cytological LSIL is also higher in older women.

Examination of factors predictive of regression was limited in our study, since few women had persistent LSIL. However, our analysis stressed the importance of time-dependent HPV status compared with HPV status measured only at baseline. A negative HPV test undertaken at a subsequent visit shows a good likelihood that LSIL has regressed. Recent recommendations by the American Society for Colposcopy and Cytology suggest that HPV testing 12 months after diagnosis with LSIL can be helpful in the follow-up of young women.[8] Others have also suggested that HPV testing might be beneficial, if cost effective, since LSIL in women with persistent viral infection was more likely to either persist or progress to HSIL.[3,21] In one study,[22] detection of high-risk types of HPV DNA was a better predictor for the development of HSIL than the detection of LSIL. In our study, there was a predominance of high-risk HPV types, and we have shown no differences in the phylogenetic groups in predicting regression. We had too few patients with low-risk HPV types only to comment on risk for this group.

Multiple HPV types seemed to have the strongest association with LSIL persistence, even when compared with HPV 16 or HPV 16-like infections. The strong inverse relation between multiple HPV types and regression suggests that some global immune defect results in the retention of multiple HPV types and LSIL changes. Certainly, multiple-type infections are common in HIV-infected women with documented immunosuppression.

Few prospective studies have examined the factors associated with regression. Although we did not note an association with demographic or behavioural factors,[23–26] our study was limited by the small number of young women in our cohort who did not regress. Host immune responses might be more important than behaviour early in the natural history of HPV.[27]

Rates of regression were closely similar in young women in whom LSIL was histologically confirmed and in those who were diagnosed solely on the basis of cytology. Although controversy continues as to whether unconfirmed cytological LSIL sometimes represents a missed lesion on biopsy or an overcall on cytology, our findings suggest that cytological diagnosis of LSIL in an adolescent is specific. Additionally, we noted no difference in time to regression between a cytological diagnosis of condyloma and CIN1, lending support to the inclusion of both in the Bethesda categorisation of an LSIL diagnosis. Our finding that biopsy did not affect the rate of regression might have been limited by the small number of lesions actually biopsied.

A limitation of our study was the exclusion of women who were shown to have HSIL on histology at their baseline LSIL visit. When we recalculated our probability estimates to include these women, we noted that exclusion of these women at baseline had little effect on our estimates. National data lend support to the notion that there is little risk of progression of HSIL to invasive cancer in this age group.[28] Another limitation was the difficulty in generalising our findings to women attending inner city clinics with high rates of sexually-transmitted infections and low rates of compliance, where follow-up is sometimes difficult and HIV infection can be underdiagnosed. Although we studied a population with high rates of pregnancy and substance use (data not shown over time), our follow-up rate was high. HIV screening in our cohort showed no positive results.

Our data suggest that most LSILs will regress spontaneously in immunocompetent young women, lending support to a practice of monitoring these cytological lesions. Follow-up HPV status was a strong predictor of regression, but HPV status at time of LSIL diagnosis was not. The finding that persistence of multiple HPV types slows rates of regression should be examined more closely.

Contributors

A-B Moscicki substantially contributed to the conception and design, analytic approach, and lead in writing the manuscript. S Shiboski substantially contributed to conception and design, supervised all data analysis, gave final approval and did the final new analysis using methods to adjust for interval censoring. N Hills was lead in statistical analysis, drafting the statistical section and results and gave final approval. K Powell substantially contributed to data collection, the methods section, and gave final approval. N Jay substantially contributed to data collection and critically reviewing the draft and gave final approval. E Hanson substantially contributed to data collection and critical review of the draft and gave final approval. S Miller substantially contributed to the conception and management of the study, critical review of the manuscript, and gave final approval. L Conjura-Clayton substantially contributed to the data management, questionnaire development, critical review of the manuscript, and gave final approval. S Farhat substantially contributed to the development of the HPV detection methods, did all the experiments, contributed to the draft of the manuscript, and gave final approval. J Broering substantially contributed to the methodological design, data management, questionnaire development, and gave final approval. T Darragh substantially contributed to the design of the study, reviewed all cytology and pathology, and gave final approval.

Conflict of interest statement

None declared.

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ANNEXURE P/9

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Natural history of cervical squamous intraepithelial lesions: A meta-analysis

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***Objective*: To define the strengths and weaknesses of existing research on the natural history of cervical squamous intraepithelial lesions (SIL) and to estimate rates of progression and regression without treatment.**

***Data Sources*: Studies of women whose cervical smears showed squamous atypia or worse and who were observed for a minimum of 6 months were identified by a search of MEDLINE from 1966 to 1996, Current Contents, the Federal Research in Progress database, and references of review articles and identified studies, and by experts in the field.**

***Methods of Study Selection*: Fifteen of 81 studies were eligible for data extraction. To be eligible, studies had to report a minimum of 6 months' follow-up without treatment; relate entry cytologic findings to outcomes; and report entry cytologic findings so that the study population could be stratified into categories of atypical cells of undetermined significance (ASCUS), low-grade SIL, or high-grade SIL. Studies published before 1970 were excluded.**

***Tabulation, Integration, and Results*: Eligible studies, representing 27,929 patients, were stratified according to entry cytologic findings. The following rates of progression to high-grade SIL at 24 months were found: ASCUS, 7.13% (95% confidence interval [CI] 0.8%, 13.5%); low-grade SIL, 20.81% (6.08%, 35.55%); and high-grade SIL, 23.37% (12.82%, 32.92%). The following rates of invasive cancer at 24 months were found: ASCUS, 0.25% (0%, 2.25%); low-grade SIL, 0.15% (0%, 0.71%); and high-grade SIL, 1.44% (0%, 3.95%). The following rates of regression to normal were found: ASCUS, 68.19% (57.51%, 78.86%); low-grade SIL, 47.39% (35.92%, 58.86%); and high-grade SIL, 35.03% (16.57%, 53.49%). Study heterogeneity was not explained by regression analysis of study level variables.**

***Conclusion*: Our findings for borderline and low-grade abnormal cervical cytologic results suggest a relatively low risk of invasive cervical cancer with observation up to 24 months and support the clinical policy of early colposcopy for high-grade lesions. (Obstet Gynecol 1998;92:727–35.**

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Cervical cytology has been extraordinarily successful in reducing mortality from cervical cancer when used in organized screening programs, and, although randomized trials of cervical cytologic screening have never been conducted, its effectiveness is considered well established.[1] The use of cervical cytology for screening and prevention of cervical cancer is based on the premises that cervical cancer develops gradually in most women, that cellular precursors to cancer and localized cancers can be detected by cervical cytology, and that treatment of these findings will reduce mortality from the disease.[2]

It is estimated that approximately 75% of women in the United States had a Papanicolaou smear in the past 3 years.[3] The national prevalence of abnormal cervical cytology can be estimated on the basis of data from Planned Parenthood clinics and the Breast and Cervical Cancer Program,[4,5] with the caveat that these groups may be at higher risk than the general population. Two percent to 5% of cervical smears (perhaps 600,000 to 1.5 million annually) will have abnormal results other than reactive or inflammatory changes. Among these abnormal Papanicolaou smears, 90% or more will be categorized as borderline changes such as atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesion (low-grade SIL).[4,5] Decisions regarding evaluation, treatment, and follow-up for these women have substantial implications for clinical decision making, health services planning, and allocation of resources.

General consensus exists regarding appropriate examination and treatment of women with smears indicating early localized cancers and high-grade SIL[6–8]; however, numerous questions remain about the appropriate examination, treatment, and follow-up of women with low-grade abnormalities on cervical smears.[6,9–14] Many of these questions derive from controversies regarding the natural history of borderline changes and low-grade cytologic abnormalities. There is growing agreement that a large proportion of low-grade abnormalities detected by cervical cytology will regress spontaneously,[6] but several investigators and clinicians have expressed concerns that less aggressive approaches to examination and treatment of women whose cytologic results show low-grade abnormalities will result in increased rates of invasive cervical cancers.[15,16] Some investigators argue that higher-grade cervical dysplasia does not evolve from low-grade dysplasia, but might coexist or occur de novo in women infected with high-risk types of human papillomavirus.[17] Uncertainty regarding the risks of observation contributes to controversy about examination and treatment of women with low-grade cytologic findings.

Better understanding of the natural history of low-grade cervical SIL could contribute substantially to evidence-based clinical policies for the examination and treatment of women with low-grade abnormalities on cervical smears. Numerous observational studies[18–50] and one randomized trial[51] have evaluated the course of untreated cervical cytologic abnormalities. These studies have not produced uniform results, contributing to the controversy over patient care. To define more clearly the strengths and weaknesses of existing research, and to estimate rates of progression and regression for untreated cervical intraepithelial lesions, we conducted a meta-analysis of English language studies published between 1970 and 1996.

Data Sources

All studies in which women with cervical smears showing squamous atypia or worse were observed for a minimum of 6 months before treatment were initially eligible for inclusion. A MEDLINE search of the English language medical literature was conducted for the years 1966 to 1996, using the medical subject headings cervix neoplasms, vaginal neoplasms, vaginal smears, atypia, cervix dysplasia, cervix carcinoma, colposcopy, patient follow-up, and natural history. Searches of the Federal Research in Progress database and Current Contents were also conducted. Additional potentially relevant studies were identified from review articles, the references of identified studies, and by experts in the field. We attempted to contact the authors of all studies selected for the analysis and inquired whether they knew of additional relevant published or unpublished studies.

Study Selection

After initial identification of potentially relevant studies, all studies were reviewed in detail by one of the authors (J.M. or J.N.), and additional exclusion criteria were applied. Because our inquiry focused on the natural history of cervical intraepithelial lesions (and not on the effect of current treatment), no initial limitation was placed on the age of the studies reviewed. However, after review and attempted stratification of cytologic classifications used, studies published before 1970 were excluded because substantial changes in terminology of cervical cytology made stratification of these studies by entry cytology and comparison of histologic findings with more recent studies uncertain.[52] Studies in which subjects' entry cytology could

not be related to outcome cytology or histology were also excluded. For studies that mixed categories of entry cytology (eg, high-grade and low-grade abnormalities) so that separate categories corresponding to the Bethesda System[53] could not be analyzed, we attempted to contact the authors to provide data by category. Studies for which this stratification was not provided were excluded.

Data Extraction and Analysis

Eligible studies were abstracted by two of the authors (J.M. and J.N.), according to a predetermined data extraction format. Key variables included entry cytology results, follow-up time, whether biopsy was performed, and outcomes, expressed as cytologic results, colposcopy findings, or pathologic results from cervical biopsy, cone biopsy, or (rarely) hysterectomy. When mean or median follow-up time for the study group was not reported directly, it was estimated as half the total follow-up time for the study. Regression to normal was defined as negative results of follow-up cytology or results of biopsy. In most studies, the minimum standard for regression was two consecutive negative Papanicolaou smears. Progression was defined as follow-up smears or biopsies showing a higher-grade lesion than the study entry cytologic finding: for ASCUS, cytology or biopsy corresponding to low-grade or high-grade SIL, including carcinoma in situ (CIS); for low-grade SIL, any high-grade SIL including CIS; for high-grade SIL, progression to cervical intraepithelial neoplasia grade 3 (from grade 2) or CIS. Rates of invasive cancer included all reported cases of microinvasive or invasive cancer. A quality assessment instrument for studies on prognosis was adapted from Hudak et al,[54] and all studies were scored by both abstractors. Differences in quality scores were resolved by consensus. The criteria and scoring for quality assessment are shown in Table 1. Quality score differences were evaluated in single factor random effects regression models.[55]

All selected studies were stratified by entry cytology into three groups corresponding to Bethesda System categories[53]: squamous atypia or ASCUS; low-grade dysplasia, mild dyskaryosis, or low-grade SIL; and moderate to severe dysplasia, moderate to severe dyskaryosis, or high-grade SIL. Because the number of studies was small and the natural history may be similar, the ASCUS and low-grade SIL categories were also analyzed as a single group to provide greater power. Categorization of entry cytology was reviewed by a cytopathologist (L.P.H.), and corresponds to a published translation table developed by an international task force for comparison of different systems of cervical cytology terminology.[56]

Table 1. Quality Assessment Criteria and Scoring System

Criteria	Score
Case definition	
Operational definition of cases including exclusion criteria	2
Operational definition of cases but no exclusion criteria	1
No explicit definition of cases or cannot tell	0
Subject selection	
Inception cohort (defined in relationship to study entry, previous screening)	2
Survival cohort (defined study entry)	1
Survival cohort (no defined study entry, unable to define subsets, cannot tell)	0
Follow-up (extent and length)	
Follow-up of ≥ 80% of total sample for ≥ 12 months	3
Follow-up of ≥ 80% of total sample for < 12 months from study entry or ≥ 80% of subjects followed up for varying lengths of time, minimum is < 12 months	2
Follow-up of < 80% of total sample for < 12 months	1
Unclear or cannot tell	0
Outcome	
Blinded outcome criteria appropriate to the research question with potential of replicability of at least one outcome	2
Outcome criteria appropriate to the research question	1
No explicit outcome criteria or cannot tell	0
Prognostic factors	
Measurement and reporting of potential prognostic factors(s), eg, smoking, age, previous treatment	2
Measurement of potential prognostic factors but not reported or insufficient detail (eg, mean, range)	1
No measurement of prognostic factors or cannot tell	0
Analysis	
Adjusted proportions provided or appropriate multivariate techniques used to adjust for other prognostic factors	3
Crude proportions but data stratified or presented in a manner that would allow for analysis of subsets	2
Crude proportions for at least one of responses, remissions, or recurrence	1
Description of sample only, unclear regarding statistical methods used or cannot tell	0

Adapted with permission from Hudak PL, Cole DC, Haines AT. Understanding prognosis to improve rehabilitation: the example of lateral elbow pain. Arch Phys Med Rehabil 1996;77:586–93.

Random effects models[57,58] were used to estimate the pooled rates for regression to normal, progression to high-grade SIL, and progression to invasive cancer. If the estimate of between-study variance was negative, the variance was set equal to zero, resulting in a fixed

Table 2. Studies Included in Meta-analysis Stratified by Entry Cytology

Entry cytology	Reference	Year published	*n*	Percent lost to follow-up	Median follow-up (mo)	% invasive cancer	Quality score*
ASCUS	Reiter[18]	1986	241	4.8	6	0.00	7
	Hirschowitz[19]	1992	638	32.0	79†	1.61	12
	Montz[20]‡	1992	91	20.1	9†	0.00	8
	Howell[21]	1996	193	35.8	15	0.00	5
	Subtotal		1163				
Low-grade SIL	Noda[22]‡	1976	62	8.3	30	NR	4
	Campion[23]	1986	100	0.0	25	0.00	12
	Nasiell[24]	1986	555	0.0	43	0.36	10
	Robertson[25]	1988	1781	24.4	24	0.74	7
	Cooper[26]	1992	337	9.5	18	0.33	10
	Montz[20]‡	1992	203	20.1	9†	0.00	8
	Flannelly[51]‡	1994	476	12.1	12	0.00	10
	Holowaty[27]‡	1996	13,226	41.0	30	0.05	10
	Subtotal		16,740				
High-grade SIL	Noda[22]‡	1976	102	8.3	30	NR	4
	Kinlen[28]	1978	101	40.6	24	22.00	7
	Heinzl[29]	1982	2528	4.4	6	NR	6
	Nasiell[30]	1983	894	0.0	60	0.34	11
	Luthra[31]	1987	359	25.0	12	0.60	5
	Flannelly[51]‡	1994	255	12.1	12	0.00	10
	Holowaty[27]‡	1996	5787	41.0	30	0.40	10
	Subtotal		10,026				
	Total		27,929				

ASCUS = atypical squamous cells of undetermined significance; SIL = squamous intraepithelial lesions; NR = not reported.
* Quality score ranges from 0 (lowest) to 14 (highest).
† Median follow-up reported in original paper.
‡ Samples from studies with multiple entry cytologies are stratified so that there is no overlap.

effects model. For each study an exponential model was assumed, to standardize the rates at 6 and 24 months follow-up for progression and invasive cancer. Single factor random effects regression models[55] were used to determine whether identified study level variables could explain variation in rates between studies.

Tabulation, Integration, and Results

We initially screened 301 studies for inclusion in the analysis; 229 did not report 6 months' follow-up. Nine additional references were identified through review of references and contacts with experts, resulting in 81 total studies for review. Forty-seven reports were excluded after secondary review: 18 had unclear reporting of outcomes or inability to relate entry cytologic finding to outcome (cytology, colposcopy, or pathology); 12 did not meet the minimum requirement of 6 months' follow-up; four reported duplicate data from other more complete reports; three were review articles; and ten were not follow-up studies.

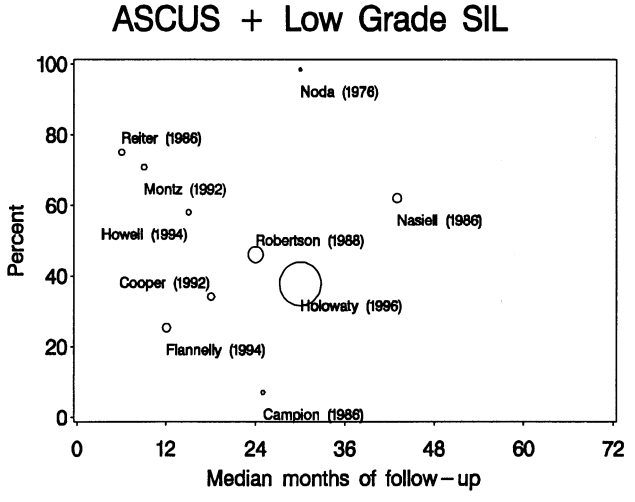
Of the remaining studies, 14 were excluded because of publication before 1970[32–45] and five because entry cytology was mixed and could not be separated and connected to outcomes.[46–50] After these exclusions, 15 reports[18–31,51] remained eligible for the analysis; 14 were published in peer-reviewed journals and one was a doctoral dissertation.

Eligible studies, representing 27,929 patients, are listed in Table 2, categorized by entry cytology. Sample sizes were between 62 and 13,226 subjects and follow-up was 6 to 79 months, with loss to follow-up from 0 to 41%. Study populations came from Canada, India, Japan, Sweden, the United Kingdom, and the United States. For some studies, entry cytology was the woman's first abnormal smear.[18,19,24,26,30] In one study,[23] three consecutive abnormal smears were required before study entry. Most studies did not specify screening history before study entry. Follow-up strategies included cytology only,[29] cytology and colposcopy for some or all subjects,[20,51] and cytology with colposcopy and biopsy for some subjects.[18,19,21–28,30,31] Studies using more than one follow-up strategy rarely reported outcomes stratified according to type of follow-up. All studies censored data after treatment from women who required treatment. Study quality scores were between 4 and 12 (Table 1).

Rates of regression to normal and progression over time for individual studies are shown relative to sample size in Figures 1 and 2. Rates of regression to normal for low-grade SIL were between 7% (median follow-up of 25 months) and 98% (median follow-up of 30 months).

Rates of progression from low-grade SIL to high-grade SIL were between 1.6% (median follow-up of 30 months) and 40% (median follow-up of 12 months). Rates of progression from low-grade SIL to invasive cancer were between 0 and 0.74%.

We calculated the following pooled rates for regression to normal: ASCUS, 68.19% (95% CI 57.51%, 78.86%); low-grade SIL, 47.39% (95% CI 35.92%, 58.86%); ASCUS and low-grade SIL combined, 52.89% (95% CI 42.33%, 63.45%); and high-grade SIL, 35.03% (95% CI 16.57%, 53.49%). Because we found no evidence of a relationship between the proportion of subjects regressing to normal and the length of follow-up, pooled regression rates were estimated without regard to follow-up time. We calculated the following pooled rates for progression: ASCUS at 6 months, 1.97% (95% CI 0%, 4.28%); ASCUS at 24 months, 7.18% (95% CI 0.80%, 13.50%); low-grade SIL at 6 months, 6.56% (95% CI 1.04%, 12.08%); low-grade SIL at 24 months, 20.81% (95% CI 6.08%, 35.55%); ASCUS and low-grade SIL combined at 6 months, 7.00% (95% CI 2.57%, 11.30%); both combined at 24 months, 21.50% (95% CI 9.87%, 33.20%); high-grade SIL at 6 months, 6.84% (95% CI 3.15%, 10.53%); and high-grade SIL at 24 months, 23.37% (95% CI 12.82%, 33.92%). We calculated the following pooled rates for invasive cancer: ASCUS at 6 months, 0.06% (95% CI 0%, 2.07%); ASCUS at 24 months, 0.25% (95% CI 0%, 2.25%); low-grade SIL at 6 months, 0.04% (95% CI 0%, 0.61%); low-grade SIL at 24 months, 0.15% (95% CI 0%, 0.71%); ASCUS and low-



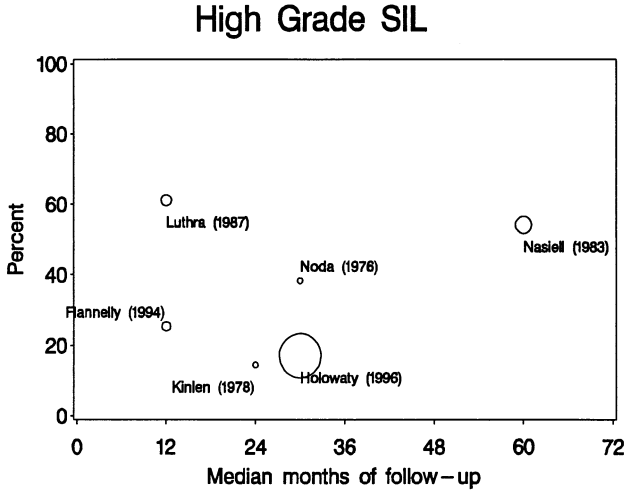
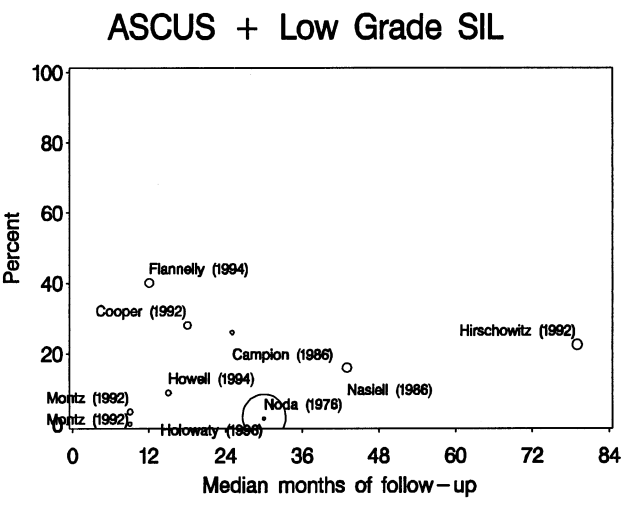


Figure 1. Regression to normal over time. Symbol size is proportional to sample size. ASCUS = atypical squamous cells of undetermined significance; SIL = squamous intraepithelial lesion.



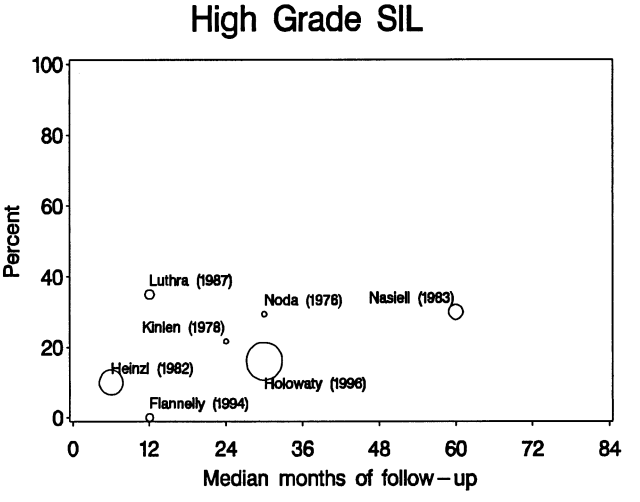


Figure 2. Progression over time. Symbol size is proportional to sample size. ASCUS = atypical squamous cells of undetermined significance; SIL = squamous intraepithelial lesion.

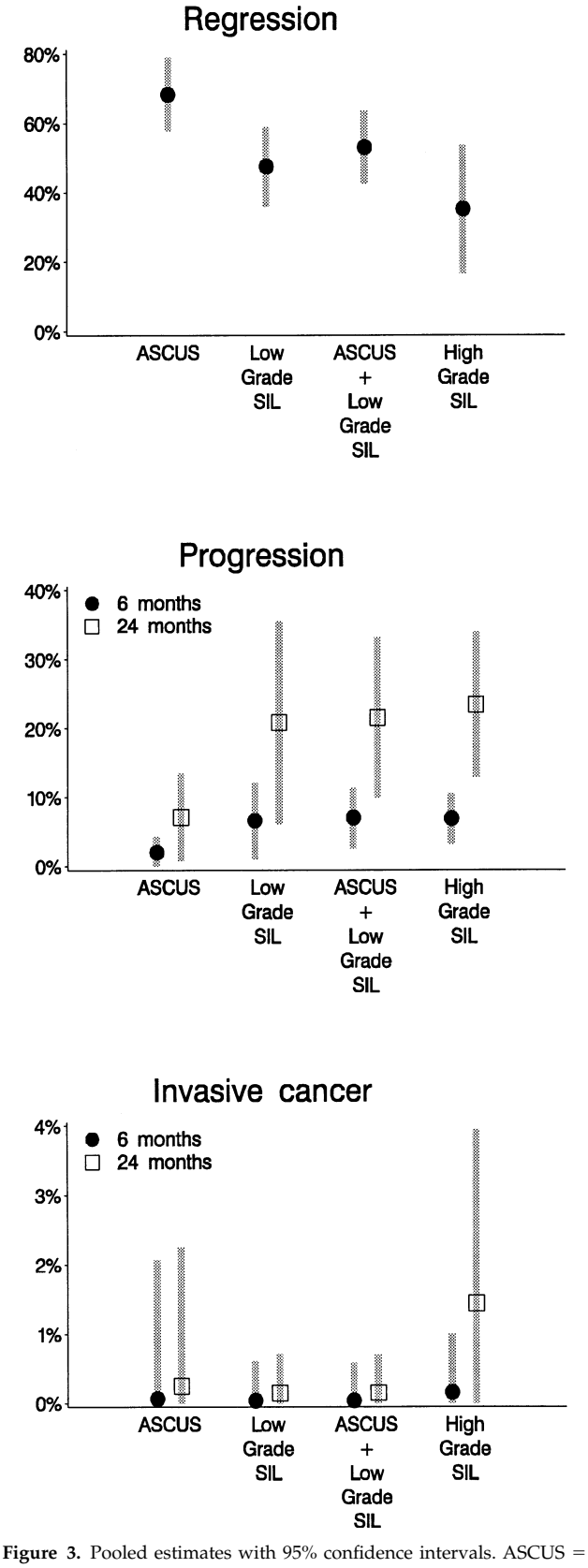


Figure 3. Pooled estimates with 95% confidence intervals. ASCUS = atypical squamous cells of undetermined significance; SIL = squamous intraepithelial lesion.

grade SIL combined at 6 months, 0.04% (95% CI 0%, 0.59%); both combined at 24 months, 0.15% (95% CI 0%, 0.70%); high-grade SIL at 6 months, 0.15% (95% CI 0%, 1.00%); and high-grade SIL at 24 months, 1.44% (95% CI 0%, 3.95%). These rates are shown with their 95% confidence intervals in Figure 3. All estimates are based on random effects models, except progression to cancer for ASCUS and low-grade SIL, in which between-study variance was negative, and fixed effects models were used.

Estimated rates for progression at 24 months were between 7.13% for ASCUS and 20.81% for low-grade SIL. The progression rate for invasive cancer at 24 months was highest for high-grade SIL (1.44%) and lowest for low-grade SIL (0.15%). Regression rates were highest for ASCUS (68.19%) and lowest for high-grade SIL (35.03%).

Single factor random effects regression analysis was used to determine whether study level variables contributed significantly to between-study variability in rates of regression to normal, progression, and invasive cancer. The following variables were included: performance of biopsy, duration of follow-up, percentage of subjects lost to follow-up, mean or median age, and quality score. None of these variables accounted for variation in rates of progression or regression of cervical dysplasia in the analysis, except for study quality score. For high-grade SIL, study quality was inversely related to progression at 6 and 24 months. For ASCUS and low-grade SIL combined, regression to normal was inversely related to quality score.

Discussion

Although reviews on the natural history of untreated cervical dysplasia have been published previously,[59,60] ours is the first to our knowledge, based on our literature review, to apply the techniques of meta-analysis to the English language literature on this topic. Studies of women whose cervical smears showed squamous atypia or worse and who were observed for a minimum of 6 months were identified by a search of MEDLINE from 1966 to 1996, Current Contents, the Federal Research in Progress database, and references of review articles and identified studies, and by experts in the field. We found that high-grade lesions were less likely to regress to normal and more likely to progress to invasive cancer, consistent with biologic theory on the process of cervical dysplasia.[2] Regression to normal without treatment for ASCUS or low-grade SIL was seen in about 53% of cases (95% CI 42%, 63%). Although rates of regression were not related to time in our analysis, progression to higher-grade lesions and to invasive cancer occurred more frequently after longer

periods of observation. For low-grade lesions, progression to invasive cancer after 24 months of observation was infrequent, with the upper bound of the 95% CI for low-grade SIL or for ASCUS and low-grade SIL combined less than 1%. The pooled rate of progression to invasive cancer for ASCUS was higher than that for low-grade SIL, although there was substantial overlap in the CIs. The category ASCUS could include a variety of cell types, including those with features suggestive of but not definitive of high-grade SIL,[61] which might have contributed to the higher rate of invasive cancer. The two studies reporting the highest rates of invasive cancer also had high rates of loss to follow-up.[19,28] If women in whom cancer develops were more likely to be followed up, this would result in falsely high estimates of the rate of invasive cancer. Including these studies in the analysis might have introduced bias toward higher cancer rates with observation over time.

The terms regression and progression, as used herein and in the published studies we reviewed, are inclusive of false-positive and false-negative cytologic and biopsy results. These findings are impossible to distinguish initially. With longer periods of follow-up and repeated testing, false positives and false negatives are unlikely.

Our criteria for inclusion were based on study design, not study findings. Hence, outliers were not excluded. Heterogeneity was addressed by use of random effects models. We found substantial study heterogeneity despite stratification by entry cytology. This heterogeneity was not explained by the study variables included in the regression analysis. The relationship of some rates of regression and progression to study quality score may have been a statistical artifact, as many analyses were conducted. It is likely that variability in entry criteria, methods of follow-up, outcome definitions, and other population and study design variables that were not consistently reported, contributed to study heterogeneity.

Despite the large number of studies screened, few met the criteria for meta-analysis, with most excluded because of unclear reporting of outcomes by entry cytology. Even eligible studies had substantial limitations in design and reporting. Lack of a clearly identified study group or cohort with defined screening history and information about possible risk factors at study entry was a problem for nearly all studies. Loss to follow-up was often substantial and may have biased findings. Type and interval of follow-up evaluation, duration of follow-up, and use of biopsy were highly variable and not always clearly reported. Without long-term, complete follow-up, sampling and interpretation errors for cytologic specimens are difficult to separate from regression and progression of dysplasia.

In future studies researchers should attempt to address such shortcomings. Demographic and clinical features of study subjects that might impact rates of regression and progression should be identified, including age, smoking status, screening history, and presence and type of human papillomavirus (if known). Type, interval, and duration of follow-up should be specified clearly. Regression to normal should be defined clearly. Loss to follow-up and its potential impact on results should be considered. Longer periods of follow-up for women whose borderline or low-grade cytologic changes have initially regressed would help clarify the risk of recurrence in untreated women compared with those who undergo treatment. Of 11 studies including women with ASCUS or low-grade SIL selected for our meta-analysis, only two had median follow-up longer than 36 months.

Difficulties are inherent to meta-analysis of observational studies because variation in design and methodology between studies is often greater than that seen in randomized controlled trials.[62] Because clinical decisions and health policies need to be based on existing evidence, systematic identification and review of that evidence according to explicit criteria are likely to yield more valid and reproducible results than the traditional, implicit approach.[63] Publication bias might be less likely in observational studies on prognosis than in other areas, as no study produces negative results.[64] We limited our search to studies published in English because of practical considerations, but it is possible that studies published in other languages could influence our conclusions.[65]

Our findings suggest that women with borderline and low-grade findings on cervical cytology carry a risk of progression to invasive cervical cancer over 24 months of one to two per thousand women without treatment. This risk is similar to an estimate generated by Soutter and Fletcher[60] using a different methodology. Whether this risk is considered acceptable depends on two factors: perception of risk by the policy maker, clinician, and patient, and impact of a more aggressive treatment strategy on risk reduction. In a previous decision analysis study,[10] we estimated that the impact of immediate colposcopy compared with observation by serial cytology for women with squamous atypia was approximately one invasive cancer prevented for every 10,000 women undergoing immediate colposcopy. We conclude that the findings of this meta-analysis support clinical policies that include periods of observation for borderline and low-grade lesions before invasive examination or intervention. The wide range of populations and age groups among the studies included in this meta-analysis extends the generalizability of these conclusions.

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ANNEXURE P/10

Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis

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Summary

Background Conservative methods to treat cervical intraepithelial neoplasia and microinvasive cervical cancer are commonly used in young women because of the advent of effective screening programmes. In a meta-analysis, we investigated the effect of these procedures on subsequent fertility and pregnancy outcomes.

Methods We searched for studies in MEDLINE and EMBASE and classified them by the conservative method used and the outcome measure studied regarding both fertility and pregnancy. Pooled relative risks and 95% CIs were calculated with a random-effects model and interstudy heterogeneity was assessed with Cochrane's Q test.

Findings We identified 27 studies. Cold knife conisation was significantly associated with preterm delivery (<37 weeks; relative risk 2·59, 95% CI 1·80–3·72, 100/704 [14%] *vs* 1494/27 674 [5%]), low birthweight (<2500 g; 2·53, 1·19–5·36, 32/261 [12%] *vs* 905/13 229 [7%]), and caesarean section (3·17, 1·07–9·40, 31/350 [9%] *vs* 22/670 [3%]). Large loop excision of the transformation zone (LLETZ) was also significantly associated with preterm delivery (1·70, 1·24–2·35, 156/1402 [11%] *vs* 120/1739 [7%]), low birthweight (1·82, 1·09–3·06, 77/996 [8%] *vs* 49/1192 [4%]), and premature rupture of the membranes (2·69, 1·62–4·46, 48/905 [5%] *vs* 22/1038 [2%]). Similar but marginally non-significant adverse effects were recorded for laser conisation (preterm delivery 1·71, 0·93–3·14). We did not detect significantly increased risks for obstetric outcomes after laser ablation. Although severe outcomes such as admission to a neonatal intensive care unit or perinatal mortality showed adverse trends, these changes were not significant.

Interpretation All the excisional procedures to treat cervical intraepithelial neoplasia present similar pregnancy-related morbidity without apparent neonatal morbidity. Caution in the treatment of young women with mild cervical abnormalities should be recommended. Clinicians now have the evidence base to counsel women appropriately.

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Introduction

The introduction of systematic call and recall screening programmes during the past 20 years has produced a profound decrease in the incidence of invasive cervical cancer. This trend has happened because of the treatment of pre-invasive lesions[1] detected by the screening programmes. These interventions are undertaken on asymptomatic women previously unaware of any potential or real disease. These women who are treated for cervical intraepithelial neoplasia are of reproductive age, with a mean age of about 30 years, although the disorder can take place in much younger women.[2,3] That treatment should be effective is paramount, but it should also have minimum adverse effects on future fertility and pregnancy outcomes.

Cold knife conisation, laser ablation, laser conisation, and large loop excision of the transformation zone (LLETZ; also known as LEEP, or loop electrosurgical excisional procedure)[4,5] are all conservative methods of treatment used to remove or destroy the transformation zone containing abnormal cells and preserve cervical function at the same time.

Characteristics of these treatments are well described and established in published work.[6] LLETZ, laser excision, and laser ablation are usually done under local anaesthesia in an outpatient setting, whereas cold knife cone biopsy needs general anaesthesia and hospital care. Theoretically, the excisional techniques (cold knife conisation, laser conisation, LLETZ) are better than the destructive techniques (laser ablation), because they allow a comprehensive histological investigation of the extirpated tissue and entire transformation zone with precise assessment of excision margins. Ablative techniques destroy the epithelium of the transformation zone and preclude histological investigation; therefore, accurate pre-treatment biopsy samples are needed at a separate initial visit. LLETZ is by far the most popular procedure,[4] by combining all the advantages of the excisional techniques mentioned above, together with a relatively short duration, low cost, good compliance, simplicity, and an easier learning curve.

The best available evidence suggests that these methods present similarly low morbidity and are equally successful at eradicating intraepithelial lesions[6,7] and preventing invasive cervical cancer.[8–10] However, the existing data for future fertility and pregnancy outcomes are conflicting.

Observational studies have indicated that these treatments could have adverse effects on fertility and pregnancy outcomes, although their conclusions are usually equivocal, perhaps due to the weakness

	Participants*		Matching factors	Procedure	Cone size	Outcomes	
	Treated	Untreated				Pregnancy	Fertility
Jones et al, 1979[42]	66–83	264	Age, parity, social class, date of delivery	Cold knife conisation	n/a	Preterm delivery, caesarean sections, precipitous delivery, low birthweight, perinatal mortality	..
Praest et al, 1979[51]	29	82	Self-matching†	Cold knife conisation	n/a	Low birthweight	..
Weber et al, 1979[44]	41–64	43–91	Partly age, parity, and partly self-matching	Cold knife conisation	n/a	Low birthweight, caesarean sections	Fertility, time to conceive
Buller et al, 1982[45]	46	79	Self-matching	Cold knife conisation	n/a	Preterm delivery, caesarean sections	Fertility
Larsson et al, 1982[49]	164–197	268–284	Self-matching	Cold knife conisation	Large cones; high proportion of radical cones	Preterm delivery, perinatal mortality, caesarean sections	..
Ludviksson et al, 1982[50]	83	79	Age, parity, date of delivery	Cold knife conisation	Mean depth 21 mm (70% of cones <25 mm)	Preterm delivery, precipitous delivery	..
Kristensen et al, 1985[47]	85	12 792	Women who delivered in same hospital during study	Cold knife conisation	n/a	Preterm delivery, low birthweight	..
Kuoppala et al, 1986[43]	62	62	Age, parity	Cold knife conisation	n/a	Preterm delivery, perinatal mortality, precipitous delivery, caesarean sections	..
Kasum et al, 1991[46]	68	68	Date of delivery	Cold knife conisation	n/a	Preterm delivery	..
Kristensen et al, 1993[48]	130	14 062	Women who delivered in same hospital during study	Cold knife conisation	n/a	Preterm delivery	..
Van Rooijen et al, 1999[41]	236	472	Age, parity, year of delivery	Laser ablation	Depth ⩾5 mm (most cases 5–7 mm)	Preterm delivery, low birthweight, caesarean sections	..
Hagen et al, 1993[38]	56	112	Age, parity	Laser conisation	Mean depth 15 (range 3–25) mm	Preterm delivery, caesarean sections, pPROM	..
Sagot et al, 1995[37]	53	59	Self-matching	Laser conisation	A) Depth 10–20 mm, diameter 20–30 mm, mean volume 5 cm^3 B) Depth 8–18 mm, diameter 12–16 mm, mean volume 2 cm^3	Preterm delivery, caesarean sections, pPROM	..
Bekassy et al, 1996[36]	250	250	Age, parity, time of delivery	Laser conisation (miniconisation)	Depth 5–7 mm	Preterm delivery, low birthweight, caesarean sections, precipitous delivery, perinatal mortality	..
Raio et al, 1997[35]	64	64	Age, parity, smoking, marital status, social class, history of preterm delivery	Laser conisation	Mean depth 11 (range 5–15) mm (preterm), 8 (3–17) mm (not preterm)	Preterm delivery, caesarean sections, pPROM	..
Blomfield et al, 1993[29]	40	80	Age, parity, ethnic group	LLETZ	Mean depth 10 (range 7–16) mm	Preterm delivery, low birthweight, caesarean sections, NICU admission, perinatal mortality	..
Haffenden et al, 1993[28]	152	152	Age, parity	LLETZ	n/a	Preterm delivery, low birthweight, caesarean sections, precipitous delivery, perinatal mortality	..
Braet et al, 1994[27]	78	78	Age, parity, smoking	LLETZ	Loop size: depth 15 mm, diameter 20 mm	Preterm delivery, low birthweight, caesarean sections, perinatal mortality, pPROM	..
Bigrigg et al, 1994[34]	72–250	62–250	Age, geographic area	LLETZ	n/a	Perinatal mortality	Fertility, time to conceive, number of pregnancies
Cruickshank et al, 1995[32]	127–149	283–298	Age, parity, smoking, height, partner's social class	LLETZ	n/a	Preterm delivery, low birthweight, caesarean sections, precipitous delivery, perinatal mortality	Fertility, intention to conceive, number of pregnancies
Turlington et al, 1996[33]	12–15	17–21	Age, parity	LLETZ	n/a	Perinatal mortality	Fertility, intention to conceive, number of pregnancies
Paraskevaidis et al, 2002[25]	28	28	Age, parity, smoking, multiple pregnancies, history of preterm delivery	LLETZ	Mean depth 13 (SD 1·8) mm, mean diameter 21 (2·1) mm	Preterm delivery, low birthweight, caesarean sections, precipitous delivery, NICU admission	..
Tan et al, 2004[26]	119	119	Age, parity	LLETZ	n/a	Preterm delivery, caesarean sections	..
Samson et al, 2005[31]	558–571	558–571	Age, parity, smoking, year of delivery	LLETZ	Mean depth 7 mm (preterm), 7 mm (not preterm); mean diameter 18 mm (preterm), 20 mm (not preterm)	Preterm delivery, low birthweight, NICU admission, pPROM, caesarean sections	..
Spitzer et al, 1995[40]	15–333	34–333	Age, parity (from the prelaser interval of the same women)	Laser conisation, laser ablation	n/a	Preterm delivery	Fertility, number of pregnancies
Forsmo et al, 1996[39]	87 (65 laser conisation, 22 laser ablation)	174 (130 laser conisation, 44 laser ablation)	Age, parity, place of delivery	Laser conisation, laser ablation	n/a	Low birthweight, perinatal mortality	..
Sadler et al, 2004[30]	581–652 (278 LLETZ, 105 laser conisation, 223 laser ablation)	256–426	Women who became pregnant after a colposcopy visit but before treatment; age, smoking, ethnic origin, history of preterm delivery, interhospital transfer, parity	LLETZ, laser conisation, laser ablation	Mean diameter 14 (SD 6·1) mm, LLETZ; 14 (4·6) mm, laser conisation; 14 (5·7) mm, both	Preterm delivery, pPROM and preterm delivery, spontaneous labour and preterm delivery	..

*Ranges represent different number of cases and controls for every outcome in the same study. †Self-matching=intrawoman comparison before and after treatment.

Table 1: **Characteristics of the included studies**

associated with small sample sizes. We have not found any published randomised controlled trials comparing pregnancy outcome between treated and untreated women in published work. Because of the premalignant nature of the condition treated, a randomised trial might not ever be undertaken. Thus, the best available level of evidence on this subject may be provided by a systematic review and meta-analysis of the controlled observational studies, which we present here.

Methods

Types of studies, interventions, and inclusion and exclusion criteria

We included all the studies that compared obstetric outcomes in pregnant women with or without a previous conservative intervention on the cervix. The considered intervention was treatment of cervical intraepithelial neoplasia or stage I A1 cervical cancer by conservative methods (ablative [laser ablation] or excisional [cold knife conisation, LLETZ, laser conisation]). Studies without an untreated control group[11–18] were excluded. Studies including different treatment methods (eg, LLETZ and cold knife conisation) were also excluded, if the outcomes for each treatment method were not reported separately.[19,20] Finally, we also excluded studies of treatment undertaken during pregnancy.[21]

Types of outcome measures

The outcome measures studied were related either to fertility or pregnancy outcome. Fertility outcomes included conception rates, number of pregnancies, and time to conception. The pregnancy outcomes were either maternal or fetal. Maternal outcomes included preterm delivery (<37 weeks), caesarean section rates, precipitous labour (<2 h), and preterm spontaneous rupture of membranes (pPROM). Fetal outcomes included low birthweight (<2500 g), perinatal mortality, and neonatal intensive care unit (NICU) admission.

Data collection and statistical analysis

We searched two electronic databases (MEDLINE and EMBASE) and targeted reports published between 1960 and 2004. The keywords used were "cervical intraepithelial neoplasia (CIN)", "cervical neoplasm", "large loop excision of the transformation zone (LLETZ)", "loop electrosurgical excisional procedure (LEEP)", "cold knife conisation", "laser ablation-destruction", "laser conisation-excision", and "fertility and pregnancy". There was no language restriction. Additionally, references of the retrieved articles and proceedings of the relevant conferences were hand-searched to identify any articles missed by the initial search or any possible unpublished data. Since no unpublished studies could be identified, we explored the possible existence of publication bias by funnel plots and by the trim and fill method that estimates the number and outcomes of potential missing studies and adjusts the meta-analysis to incorporate these theoretically missing studies.[22]

The literature search, inclusion and exclusion criteria, and extraction of the data were independently undertaken and verified by each one of the two primary investigators (MK, GK). Results were then compared and a consensus was reached, with the involvement (in case of discrepancies or disagreements) of a third investigator (PMH) if necessary. From every study, we retrieved the number of cases and controls in which every outcome was observed. We analysed data by using a random-effects model.[23] Relative risks and 95% CIs were calculated with Revman 4.2 software. Heterogeneity among studies for every outcome was assessed by use of a Cochrane Q test.[24]

Additional analyses

The recorded differences in pregnancy outcome could have been confounded by discrepancies in the compared study populations. To assess this possibility, we did subgroup meta-analyses of relevant studies with matching for at least three factors (age, parity, and smoking), studies that applied self-matching, studies without matching or matching for less than these three factors, and studies after exclusion of those that had used self-matching. A further analysis of the dimensions of the excised tissue was undertaken, which included the main findings of the individual studies as well as a subgroup analysis of the risk of preterm delivery according to the depth of the excised tissue.

	Studies (number of participants)	Positive cases/ total cases (%)	Positive controls/ total controls (%)	Pooled relative risk (95% CI)	Hetero-geneity (p)
LLETZ					
Preterm delivery	8 (3141)	156/1402 (11%)	120/1739 (7%)	1·70 (1·24–2·35)	0·14
Low birthweight	6 (2188)	77/996 (8%)	49/1192 (4%)	1·82 (1·09–3·06)	0·11
Caesarean delivery	7 (2463)	181/1137 (16%)	223/1326 (17%)	0·88 (0·71–1·09)	0·36
Precipitous delivery	3 (807)	27/329 (8%)	27/478 (6%)	1·26 (0·75–2·11)	0·99
pPROM	3 (1943)	48/905 (5%)	22/1038 (2%)	2·69 (1·62–4·46)	0·60
NICU admission	3 (1318)	88/639 (14%)	73/679 (11%)	1·25 (0·93–1·67)	0·57
Perinatal mortality	3 (1418)	5/689 (1%)	1/729 (<1%)	3·40 (0·62–18·63)	0·82
Laser conisation					
Preterm delivery	6 (1488)	76/562 (14%)	89/926 (10%)	1·71 (0·93–3·14)	0·01
Low birthweight	2 (695)	21/315 (7%)	24/380 (6%)	1·23 (0·39–3·94)	0·041
Caesarean delivery	4 (908)	52/423 (12%)	57/485 (12%)	1·16 (0·64–2·09)	0·049
pPROM	3 (729)	32/217 (15%)	29/512 (6%)	2·18 (0·77–6·16)	0·033
Perinatal mortality	1 (195)	4/65 (6%)	1/130 (1%)	8·00 (0·91–70·14)	NE
Laser ablation					
Preterm delivery	3 (1583)	53/588 (9%)	100/995 (10%)	0·87 (0·63–1·20)	0·59
Low birthweight	2 (774)	13/258 (5%)	31/516 (6%)	0·84 (0·45–1·58)	0·83
Caesarean delivery	1 (708)	22/236 (9%)	56/472 (12%)	0·79 (0·49–1·25)	NE
PPROM	1 (599)	10/210 (5%)	15/389 (4%)	1·23 (0·56–2·70)	NE
Perinatal mortality	1 (500)	2/250 (1%)	3/250 (1%)	0·67 (0·11–3·96)	NE
Cold knife conisation					
Preterm delivery	8 (28 378)	100/704 (14%)	1494/27674 (5%)	2·59 (1·80–3·72)	0·12
Low birthweight	4 (13 490)	32/261 (12%)	905/13229 (7%)	2·53 (1·19–5·36)	0·054
Caesarean delivery	4 (1020)	31/350 (9%)	22/670 (3%)	3·17 (1·07–9·40)	0·075
Perinatal mortality	3 (935)	10/325 (3%)	9/610 (1%)	1·89 (0·77–4·65)	0·68

NE=not estimable.

Table 2: **Meta-analysis of studies comparing obstetric outcomes after LLETZ, laser conisation, laser ablation, and cold knife conisation with controls**

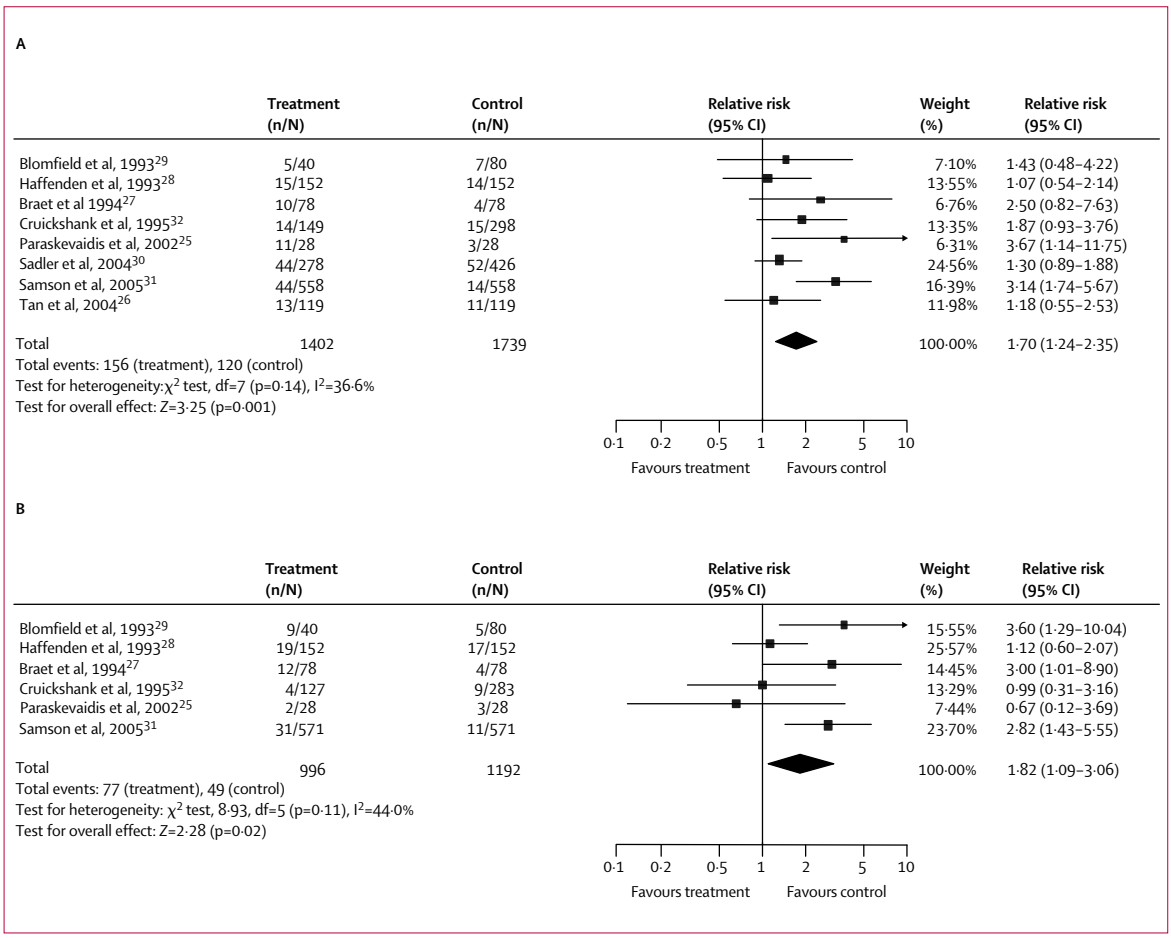


Figure 1: **Forest plot showing association between LLETZ and (A) preterm delivery and (B) low birthweight**

Role of the funding source

There was no funding source for this meta-analysis. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 27 studies that fulfilled the inclusion criteria,[25–51] all of which studied retrospective cohorts. Ten studies reported the effects of LLETZ,[25–34] seven of laser conisation,[30,35–40] four of laser ablation,[30,40,41] and ten of cold knife conisation.[42–51] Table 1 summarises the characteristics of these studies, stratified according to the method used and by chronological order. Four of the studies on cold knife conisation[44,45,49,51] and one on laser conisation[37] used self-controls and compared outcomes in the same women before and after treatment. One study[40] used selected controls matched for age and parity from the prelaser interval of the same women.

Table 2 shows the total effect of the meta-analysis for every outcome and treatment method used. Most individual comparisons did not show interstudy heterogeneity. LLETZ was associated with a significant increase in the risk of preterm delivery, low birthweight, and pPROM (figure 1). We recorded no significant differences with respect to caesarean section, precipitous labour, perinatal mortality, or NICU admission (table 2).

For laser conisation, all pooled estimates of relative risk were higher than unity but never reached significance (table 2, figure 2). However, the association between laser conisation and preterm delivery was marginally non-significant. Significant interstudy heterogeneity was seen for the laser conisation studies, which was due to one conflicting study[40] (figure 2, A). The exclusion of this outlying study reduced the heterogeneity and resulted in a significant effect (relative risk 1·91, 95% CI 1·03–3·55). The reasons for these outlying results are not clear and could be possibly caused by the study design mentioned earlier.

Laser ablation was not significantly associated with any of the outcomes studied (table 2, figure 3). Cold knife cone biopsy was associated with a significant increase in preterm delivery, low birthweight, and caesarean section (table 2, figure 4). With respect to perinatal mortality, the estimate of relative risk was

higher than 1, but was not significant. Additional forest plot data for the rest of the obstetric outcomes are available from the corresponding author on request.

The subgroup findings did not show significantly different results (webtable). Only LLETZ studies matching for age, parity, and smoking yielded a higher relative risk for preterm delivery (2·10, 95% CI 1·34–3·29) than unmatched studies (1·17, 0·74–1·86); for laser conisation, the relative risk for preterm delivery was significant (1·60, 1·03–2·50). Furthermore, the subgroup analysis after exclusion of the studies that applied self-matching did not alter our results (webtable). We saw the same tendency in studies with self-matching (four on cold knife conisation and one on laser conisation) compared with those matching for less than three factors.

A further analysis of excisional methods with respect to the dimensions of tissue removed was undertaken. Table 1 presents all available information on the dimensions of the cone in the included studies. Only a few studies investigated the association between the amount of tissue removed and adverse obsteric outcomes, and the data are scarce and inconsistent. Some data do exist for the effect of cone height in LLETZ[30,31] and laser conisation,[35,37,38] but are conflicting. Because of different comparisons, thresholds, and statistical methods, meta-analytical pooling was often not possible.

Nevertheless, in three studies,[30,31,35] the risk of preterm delivery associated with LLETZ or laser conisation was specified according to the depth of the excised cone (less *vs* more than 10 mm). In all three studies, we recorded a significantly increased risk if the depth was more than 10 mm (pooled relative risk 2·6, 95% CI 1·3–5·3). If the cone depth was less than 10 mm, results were heterogeneous; two studies[30,35] did not identify a raised risk, whereas one[31] did show a significant association. The 95% CI of the pooled relative risk was large and included unity (1·5, 0·6–3·9; figure 5).

See **Online** for webtable

Fertility outcomes are reported in three studies after LLETZ,[32–34] one after laser conisation and laser ablation,[40] and two after cold knife conisation.[44,45] One LLETZ study[32] and one cold knife conisation study[45] did not show any relevant data for the untreated group and therefore could not fulfil the inclusion criteria. In the remaining four studies, the outcomes studied were: total pregnancies,[33,34,40] ability to conceive in women who desired pregnancy in an unspecified period,[33] and time elapsed to achieve a pregnancy.[34,44] Table 3 includes the available extracted data. None of these findings suggests any effect of conservative treatments on fertility. The differences in probability to conceive between treated and untreated women were generally negligible,[33,34,44] apart from one study[40] that revealed a significantly increased probability in the treatment group. We did

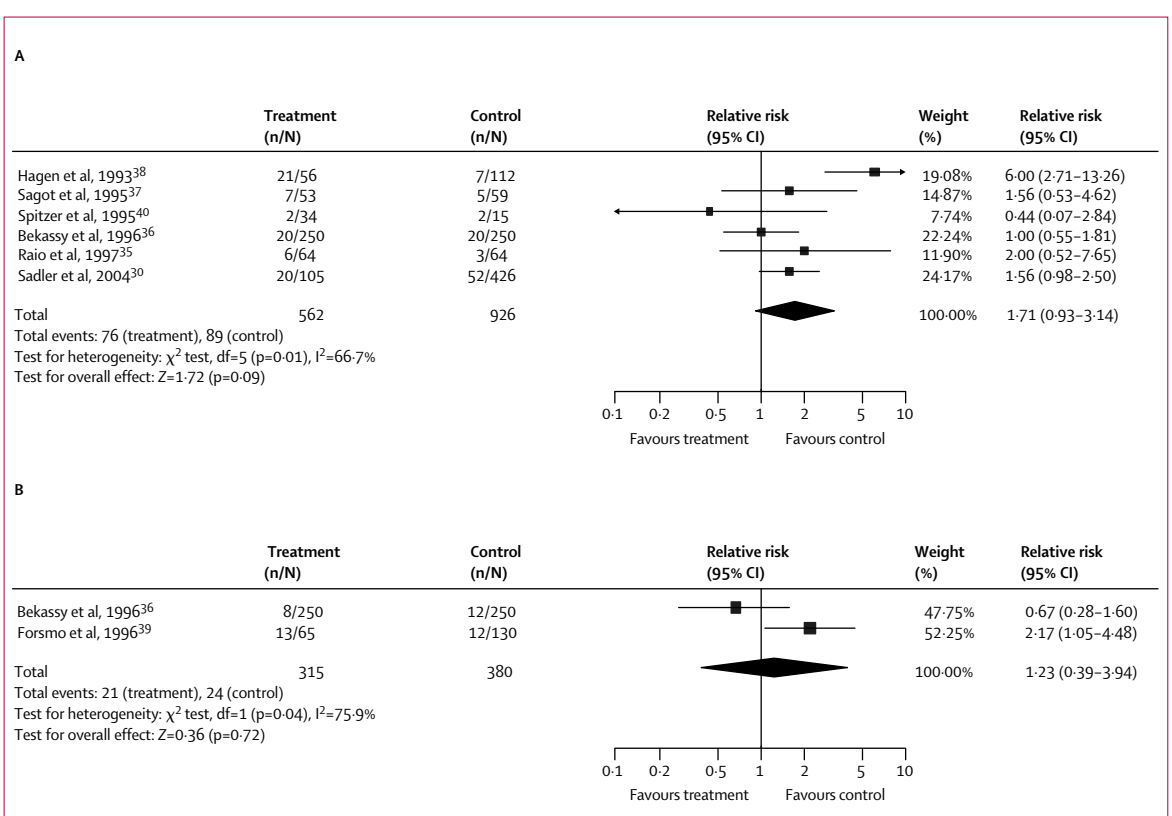


Figure 2: **Forest plot showing association between laser conisation and (A) preterm delivery and (B) low birthweight**

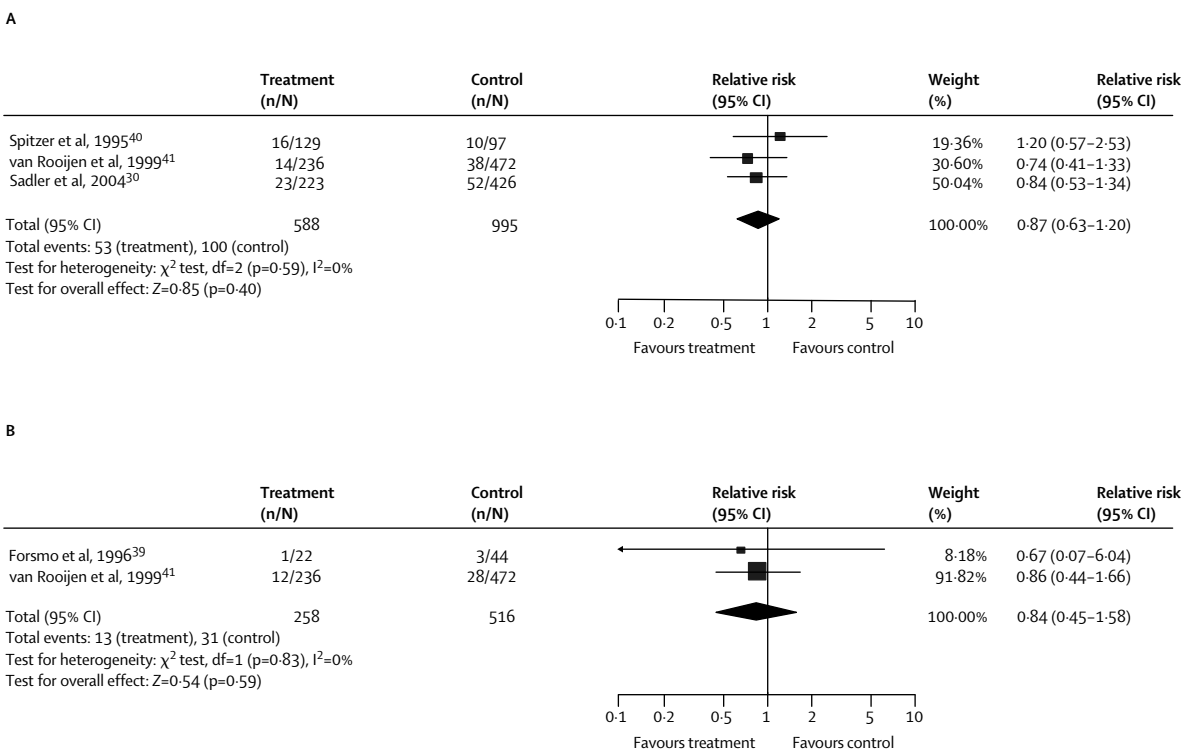


Figure 3: **Forest plot showing association between laser ablation and (A) preterm delivery and (B) low birthweight**

not undertake a meta-analysis because of clinical heterogeneity between studies in the outcome measures examined.

Funnel plots and the trim and fill method were used to explore the possibility of publication bias on the two largest comparisons—ie, preterm delivery after cold knife conisation and LLETZ, in which sufficient studies were available for statistical exploration (eight reports for each procedure). The funnel plots revealed no evidence of possible publication bias. The trim and fill analysis yielded the same conclusions for cold knife conisation without evidence of any potentially missed unpublished studies or any effect on the relative risk for preterm delivery. However, the analysis identified the potential theoretical existence of three studies, which can be assumed as existing but not published in the relevant LLETZ comparison, shifting the estimated effect to non-significance (relative risk 1·70, 95% CI 1·24–2·35 *vs* 1·32, 0·92–1·93) after incorporation of these theoretically missing studies in the meta-analysis (data not shown).

Discussion

With respect to pregnancy outcomes, our meta-analysis has revealed that cold knife conisation is associated with an increased risk of preterm delivery, low birthweight, and caesarean section rate. Likewise, the risk of preterm delivery, low birthweight, and pPROM increased significantly after LLETZ. However, our analysis of laser conisation marginally failed to detect a significant difference regarding preterm delivery, and none of the other outcomes was affected significantly. Furthermore, we recorded none of the variables to be significantly affected after laser ablation.

Most individual studies of pregnancy outcomes after conservative treatment for cervical intraepithelial neoplasia or microinvasive cervical cancer are hampered by the relative inability to detect significant differences as a result of small sample size. The combining of these existing studies reduces the chance of a type 2 error. For all treatment procedures apart from laser conisation, the comparisons show no evidence of interstudy heterogeneity, confirming consistent direction and magnitude of effect.

The scarce data for fertility outcomes in this review do not indicate any adverse effects. The number of the relevant studies, which were profoundly heterogeneous, was small and the quality of the data was weak, mainly obtained through telephone contacts, mailed questionnaires, and records in infertility clinics. Prospectively designed studies do not exist and would be very difficult to undertake. However, despite these difficulties, the available evidence suggests that fertility is not impaired after treatment for cervical intraepithelial neoplasia.

This meta-analysis of cold knife conisation has not established any new conclusions. The new and

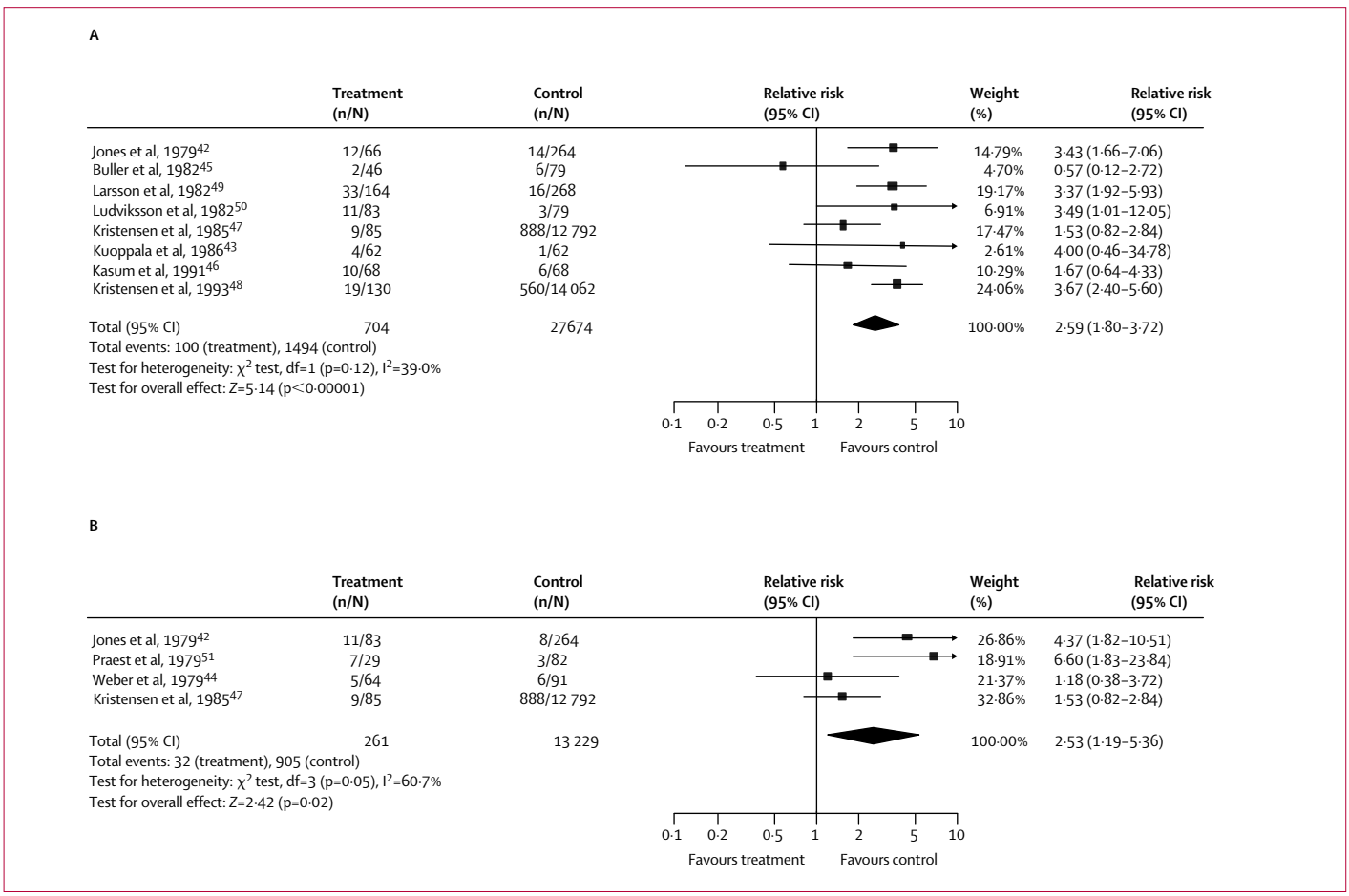


Figure 4: **Forest plot showing association between cold knife conisation and (A) preterm delivery and (B) low birthweight**

additional information concerns mainly laser conisation and more importantly, LLETZ, which has previously had equivocal information. The outcomes of LLETZ are especially important, because it is now by far the most popular treatment for cervical intraepithelial neoplasia. As a consequence, many clinicians have thought outpatient excisional procedures are not associated with any adverse obstetric morbidity and have counselled women accordingly. Early, small, low-power studies seem to have been superseded by large studies showing adverse pregnancy-related morbidity.

When combined, the results from the existing studies in our meta-analysis indicated that all the conservative excisional methods had similar unfavourable effects.

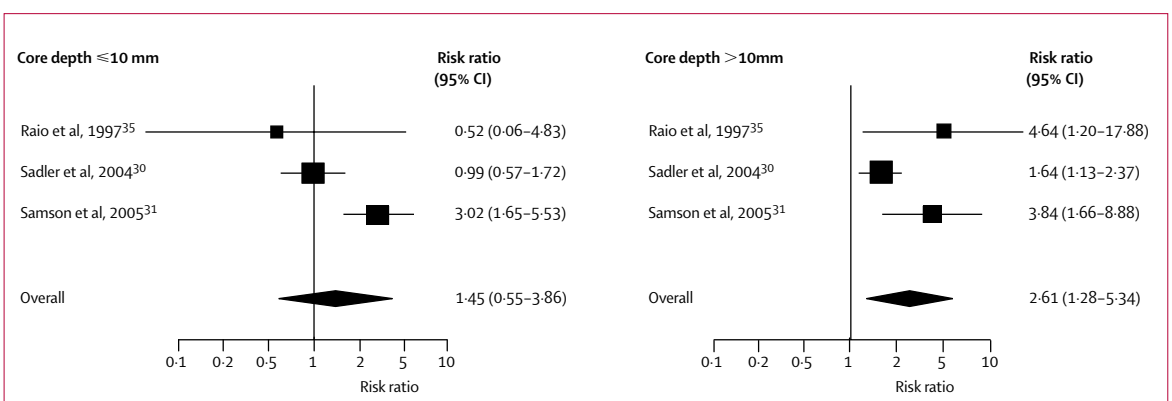


Figure 5: **Forest plot showing risk of preterm delivery associated with LLETZ or laser conisation according to cone depth**

	Control characteristics	Data source	Procedure	Fertility outcomes	Treated	Untreated	p
Weber et al, 1979[44]	Matched for age	Interview first at antenatal clinic followed by a questionnaire	Cold knife conisation	Time to conceive:			
				0–3 months	10/21	9/20	0·87
				0–6 months	12/21	11/20	0·89
				0–9 months	14/21	13/20	0·91
				0–12 months	14/21	14/20	0·82
				0–24 months	18/21	18/20	0·68
Bigrigg et al, 1994[34]	Matched for age, geographic area; all controls had negative smears	Telephone contact, mail questionnaires	LLETZ	Total number of pregnancies	194/1000	n/a	NE
				Time to conceive:			
				0–3 months	36/72	36/62	0·35
				0–6 months	61/72	51/62	0·70
				0–12 months	67/72	55/62	0·38
				0–12 months or more	72/72	62/62	..
				>1 year	7/72	12/62	0·11
				>3 years	4/72	5/62	0·56
Turlington et al, 1996[33]	Matched for age, parity; all cases and controls had abnormal smears, colposcopy, and biopsy samples with or without LLETZ	Chart review, telephone interviews, mail questionnaires	LLETZ	NPIC	11/12	17/17	0·23
				Total number of pregnancies	15/54	21/57	0·31
Spitzer et al, 1995[40]	Age, parity (from the prelaser interval of the same women)	Mail, telephone, questionnaire in person at follow-up visit	1) Laser conisation	Total number of pregnancies	67/100	28/100	<0·0001
			2) Laser ablation		210/333	149/333	<0·0001

n/a=not available. NE=not estimable. NPIC=number of pregnancies in women with intention to conceive.

Table 3: **Fertility characteristics, outcomes, and data in studies after conservative treatment for cervical intraepithelial neoplasia**

Additionally, perinatal mortality was consistently increased in treated women, although our study did not have strong enough power to confirm or exclude a definite increase in the risk of perinatal mortality.

The fact that removal or destruction of part of the cervix will affect function, especially during subsequent pregnancies, is unsurprising. One would logically expect that the more cervical tissue that is removed, the greater the effect on function might be. No study so far has revealed a discriminating variable that might allow more specific prognostication. In the subgroup meta-analysis specifying the relative risk according to the dimension of the cone, we recorded a consistent and significantly increased risk for preterm delivery if the depth of the excision exceeded a cutoff of 10 mm. However, for excisions less than 10 mm, the data from the individual studies were contradictory and heterogeneous, and therefore clear and definite conclusions could not be derived. A subgroup analysis of the data extracted from the studies examining the grade of disease or the degree of prematurity was not feasible, since very few original studies examined these variables.

The subgroup analysis revealed similar trends towards unfavourable effects. Therefore, from these data, we can conclude that our recorded results were not due to imbalances in distribution of confounding factors among the comparison groups and that the direction of effect was stable for excisional treatments. Nevertheless, we cannot exclude the possibility of biased comparison groups, since the subgroup meta-analyses were compromised by a small number of studies and by the quality of description of subgroups; therefore residual confounding cannot be ruled out. A subgroup analysis was not even feasible for some treatment methods and outcomes because no studies matched for these three confounding factors (age, parity, and smoking).

For publication bias, the funnel plot assessment has shown no significant differences for either cold knife conisation or LLETZ. The same result holds true for cold knife conisation with the trim and fill method. The trim and fill method might statistically weaken the robustness of LLETZ adverse effects.

All the original studies were retrospective, and therefore had all the limitations related to this type of study. These limitations include the possibility of confounding bias related to failure to adjust fully for all the confounding factors, and also the possibility of information bias related to failure to first correctly record and then efficiently retrieve the relevant data from the records. However, in reality, this information is the only available evidence-base at present.

Despite the limitations of this meta-analysis, mainly due to the retrospective and observational nature of the studies, our findings show that all the excisional conservative methods of treatment have some adverse pregnancy-related morbidity. Experience in colposcopy, especially in the treatment of women, is mandatory to achieve the best balance between the maximum eradication rates and the minimum deficit and disruption of cervical anatomy; therefore, therapy should always be undertaken by experienced clinicians.

The clinical implications of our findings are that women should be informed of a small risk of pregnancy-

related morbidity after excisional treatment for cervical intraepithelial neoplasia. Whether, as a consequence of this meta-analysis, women with a history of previous excision (especially those with a big excision in relation to their cervix) should be considered as high-risk in subsequent pregnancies and managed accordingly is beyond the purposes of this study.

The question of obstetric morbidity after cryocautery or cold coagulation has not been addressed because we could not find cohort studies dealing with the long-term adverse effects of these methods that met the inclusion criteria of our meta-analysis. Efficacy as well as long-term pregnancy-related consequences of these low-cost treatments should be investigated in future prospective studies.

The potential research implications of this meta-analysis include a search for the specific aspects of excisional treatment that could predispose to pregnancy-related morbidity. Disproportionately large excisions of the transformation zone (relative to the individual cervical volume or length) or excisions that include a relatively greater amount of endocervical tissue could be associated with increased risk. An ongoing prospective study investigating the proportion of the cervical volume (or the endocervical canal) excised might give an insight into different patterns of cervical function in future pregnancies, and thus possibly inform women and guide obstetric care accordingly. Wound management after excision (eg, amount or depth of diathermy damage) could be a variable that relates to increased risk.

Our findings could probably favour the initiation of cervical screening after the age of 25 years with respect to long-term obstetric outcomes.[52,53] The current vogue of excisional treatment has clearly been shown to have long-term adverse obstetric outcomes, and delay in treatment would avoid these unnecessary outcomes in a substantial proportion of women younger than 25 years. Furthermore, in young women with low-grade disease who have a very low risk of progression,[54,55] the option of surveillance should always be considered.[53]

In summary, evidence clearly indicates that excision of the transformation zone is associated with a small but real increase in risk of pregnancy-related morbidity. This information should be considered when counselling women before their consent to treatment and lends support to the philosophy of doctors not treating young women with mild abnormalities.

Conflict of interest statement

We declare that we have no conflict of interest.

Contributors

M Kyrgiou was the main author and assessor and G Koliopoulos the secondary assessor of the paper. P Martin-Hirsch and W Prendiville edited the paper. M Arbyn contributed as the epidemiological and statistical adviser, and answered the statistical questions of the reviewers. He obtained unpublished data from the corresponding authors of some of the included studies and did additional statistical analyses. E Paraskevaidis thought of the initial concept of the study, was the lead author, and edited the paper. All investigators contributed to data interpretation and preparation of the manuscript.

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ANNEXURE P/11

The Royal Society of Medicine

Review

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Will HPV vaccination prevent cervical cancer?

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Summary

We conducted a critical appraisal of published Phase 2 and 3 efficacy trials in relation to the prevention of cervical cancer in women. Our analysis shows the trials themselves generated significant uncertainties undermining claims of efficacy in these data. There were 12 randomised control trials (RCTs) of Cervarix and Gardasil. The trial populations did not reflect vaccination target groups due to differences in age and restrictive trial inclusion criteria. The use of composite and distant surrogate outcomes makes it impossible to determine effects on clinically significant outcomes. It is still uncertain whether human papillomavirus (HPV) vaccination prevents cervical cancer as trials were not designed to detect this outcome, which takes decades to develop. Although there is evidence that vaccination prevents cervical intraepithelial neoplasia grade 1 (CIN1) this is not a clinically important outcome (no treatment is given). Trials used composite surrogate outcomes which included CIN1. High efficacy against CIN1+ (CIN1, 2, 3 and adenocarcinoma in situ (AIS)) does not necessarily mean high efficacy against CIN3+ (CIN3 and AIS), which occurs much less frequently. There are too few data to clearly conclude that HPV vaccine prevents CIN3+. CIN in general is likely to have been overdiagnosed in the trials because cervical cytology was conducted at intervals of 6–12 months rather than at the normal screening interval of 36 months. This means that the trials may have overestimated the efficacy of the vaccine as some of the lesions would have regressed spontaneously. Many trials diagnosed persistent infection on the basis of frequent testing at short intervals, i.e. less than six months. There is uncertainty as to whether detected infections would clear or persist and lead to cervical changes.

Keywords

Vaccination programmes, cervical cancer

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The human papillomavirus (HPV) vaccination programme aims to prevent cervical cancer. Globally around 13.1/100,000 women are diagnosed with cervical cancer each year.[2] Typically, vaccination is offered to girls aged 9–13 years before sexual debut and naïve to HPV infection. Box 1 gives an overview of licensing and indications in Europe and the US.

Public health agencies promote the position that the vaccine has been shown to prevent cervical cancer (see Supplement 1). Not all routinely emphasise the limitations of the evidence or the uncertainties which we will discuss.

Background

A key issue for the design of trials and studies of efficacy is the complexity of the epidemiology of the HPV subtypes and the lesions used as surrogate endpoints for cervical cancer, each with their own different natural histories, prevalence and incidence and strength of association with cancer. These measures, especially if combined as composite surrogate endpoints in trials, generate new uncertainties.

i) HPV infection

There are 100+ types of the HPV: 12 of which are carcinogenic to humans, according to the International Association of Cancer Research (IARC).[4] Types vary in prevalence, as does their association with cervical cancer. HPV vaccines are licensed for use against oncogenic HPV types 16 and 18 and now 31, 33, 45, 52, 58 in Gardasil-9. Gardasil and Gardasil-9 are also licensed against non-oncogenic types 6 and 11 linked to genital warts.

The lifetime risk of an incident of HPV infection is 79%;[5] the majority of HPV infections are transient and 67% clear within one year.[6] Around 10% of women without CIN have HPV infection at any one time.[7] The mechanism of progression from HPV infection to cervical cancer and its precursors is not well understood.[4,8–11]

ii) Cervical cancer and pre-cancerous lesions as surrogate endpoints

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Key Messages.

- We do not know how well HPV vaccination will protect against cervical cancer. Trials have not focused on the outcome of cervical cancer because they had too few participants and did not follow them up for long enough: cervical cancer may take decades to develop.
- Published numbers from randomised controlled trials may overstate efficacy because: (a) testing occurred too frequently in the trials when, in real-world settings, lesions may regress spontaneously; (b) trials used composite surrogate outcomes, some of which, such as HPV-infection and CIN1, occur more frequently than others and are very unlikely to progress to cancer; and (c) subgroups were over-analysed.
- The trial populations have limited relevance and validity for real world settings: for example, women in the trials were older than the target population; we do not have enough data on the benefits in women who may have been exposed to HPV before they were vaccinated and who do not know their HPV status.
- We do not have enough data on the impact of the vaccine on CIN3, which is more likely than CIN1 and 2 to progress to cervical cancer. We also have less data on the impact on cervical disease due to any HPV type rather than just lesions due to HPV 16 and 18.
- Women should still attend regular cervical screening because efficacy in preventing cervical precursors is <100% and there are more oncogenic types than those covered by the vaccines. We have good evidence that cervical screening significantly reduces the risk of cervical cancer in women regardless of whether they have been vaccinated. The number of new cancers and deaths has decreased markedly such that cervical cancer now accounts for only 1% of cancer deaths in women in the UK (854 deaths in 2016).[1]
- Information from the trials can tell us what happens between five and nine years after vaccination, but we do not know if protection wanes after this time.
- A recent observational study provides some evidence of efficacy against CIN3+ in girls vaccinated before sexual debut. Ongoing observational studies may tell us about the long-term effect on rates of cervical cancer, but it will take many years before we have the evidence.

Box 1. Licensing and guidelines.

Licensing

- Gardasil, Gardasil-9 and Cervarix vaccines have been approved for marketing and used in females and males from the age of 9 years throughout the world to prevent cervical cancer.
- The European Medicines Agency (EMA) and US Food and Drug Administration (FDA) granted marketing approval for Gardasil in 2006, and for Cervarix in 2007 and 2009, respectively.
- Gardasil-9 was approved in 2014 by the FDA and in 2015 by the EMA, but it is not currently used in the UK.
- The EMA has licensed all three vaccines for females and males with no upper age limit. The FDA has licensed Gardasil up to age 26 and Gardasil-9 up to age 45 for females and males, and Cervarix for females only up to age 25.

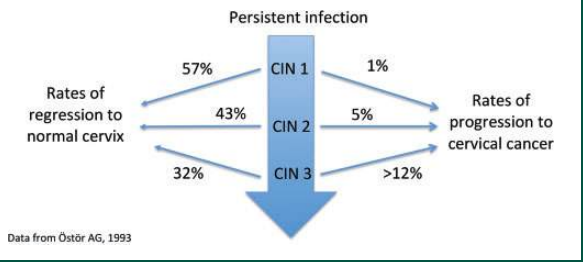
Guidelines

- The US Centers for Disease Control and Prevention recommends 'routine vaccination at age 11 or 12 years. (Vaccination can be started at age 9.) The Advisory Committee on Immunization Practices also recommends vaccination for females aged 13 through 26 years not adequately vaccinated previously'.[3]
- The UK uses Gardasil. Public Health England advises girls to be vaccinated from age 12–18 years. Immunisation Scotland offer the vaccine for girls aged 11–13 years. There is a planned roll-out to boys aged 12–13 in England and Scotland.

Estimated rates of regression and progression for CIN1, 2 and 3 are presented in Figure 1.[12] However, there remain uncertainties due to methodological issues in the epidemiological studies from which these findings originate.[12]

The IARC has acknowledged that composite endpoints in intervention studies involving CIN2 are sub-optimal[13] as CIN2 is often misclassified due to its diagnosis having lower reproducibility and validity.[14] Women with CIN2 are currently offered

Figure 1. CIN natural history.



treatment which complicates research into progression to CIN3.

CIN3 can develop via progression of CIN1 and CIN2 or directly as a result of HPV infection, so CIN1 and CIN2 may not be good predictors of progression. Rate of progression from CIN3 to invasive cancer is likely to be higher than Ostor's estimate of >12%.[12] Lifetime risk may be up to 40% without cervical screening and treatment.[15]

Aim

To describe the uncertainties generated by the design of Phase 2 and 3 efficacy trials for prevention of cervical cancer and its precursors and how they affect the interpretation of efficacy data.

Methods and analysis

We searched Embase and Medline for papers relating to blinded controlled trials of HPV vaccination in females considering efficacy against cervical cancer and its precursors. See Supplement 2 for search strategy. No trial has tested Gardasil and Cervarix vaccines head to head using clinical outcomes (rather than immunological outcomes). We reviewed 35 published papers relating to 12 published randomised blinded non-HPV vaccine-controlled Phase 2 and 3 trials of Gardasil and Cervarix conducted from 2001 to 2016 assessing efficacy against cervical cancer and its precursors (Table 1 and Figure 2). Throughout this article, we refer to trials by their protocol name as presented in bold in Table 1. But for trials 104798 and 107638, we use the name of their first authors, Konno and Zhu, respectively.

We excluded trials of the HPV 16 monovalent vaccine (as it was not licensed and data suggest it had different pharmacodynamics to Gardasil and Cervarix[16]) and the one efficacy trial of Gardasil-9 (as the control was Gardasil, not a placebo).[17] All the efficacy studies used an active vaccine (Hepatitis A) as the control, or a control containing an aluminium-adjuvant, rather than a true placebo; this in itself has raised concerns.[11] We chose to focus on randomised controlled trials as this offers the highest level of evidence and this is the evidence used for decisions by regulatory bodies and decisions on initiating vaccination programmes.

We also found 39 meta-analyses and systematic reviews of HPV vaccine efficacy; of them many are restricted to post-hoc analyses of subgroups and have inappropriately combined trials in the same analysis, e.g. for different vaccines (see Supplement 3). The 2018 Cochrane review[18] has been criticised for failing to include all relevant trials, ignoring evidence of harms and using composite endpoints with different natural histories.[19]

We compared the eligibility criteria, testing methods for HPV and cervical lesions, outcomes measures, length of follow-up, target group and subgroup definitions used in the different trials. We focused on the evidence for efficacy for CIN3+ and 12-month persistent infection which are deemed the more stringent outcome measures.

Does HPV vaccine prevent cervical cancer?

None of the trials were designed to determine efficacy or effectiveness against cervical cancer. There were no reported cases of cervical cancer in any trials; one case of vulval carcinoma was reported in the vaccinated group of FUTURE I.[48]

The time between first exposure to HPV and peak development of CIN3 is 7–10 years.[13] It takes a further 10 years or so for cervical cancer to develop according to natural history studies.[13] All trials had a mean length of follow-up of six or fewer years, apart from the HPV-023 extension with a mean follow-up of 8.9 years.

Does HPV vaccine prevent pre-cancerous lesions?

There were eight powered outcomes relating to cervical disease used across the trials, all of which were surrogates or composite surrogate outcomes (Table 2). Surrogate outcomes are biomarkers used as substitutes for clinical endpoints and used to predict an intervention's benefits. Key pre-marketing trials evaluated the effect of HPV vaccines against pre-cancerous lesions, endpoints that were accepted by authorities as a surrogate for cervical cancer. There are limitations to surrogate outcomes in general,[54] and for HPV and cervical cancer. Using composite surrogate outcomes (combining two or more surrogate outcomes together) is problematic because of differences in epidemiology and their natural history and management – see 'Background' section and

Table 1. All Phase 2 and 3 trials by vaccine and control, sponsor, country, start and end dates, number and age of participants and length of follow-up.

Vaccine and control	Trial name, NCT number (and sponsor)	Research papers	Phase	Country	Start date	End date	Number of participants	Age at enrolment	Average (mean) length of follow-up
Cervarix versus aluminium-hydroxide containing control	**HPV-001**/580299 NCT00689741 (GSK)	Harper et al.[20]	2	USA (incl. Puerto Rico), Brazil, Canada	Jan-01	Apr-03	1113	15–25	Up to 27 months (average not given)
Cervarix versus placebo aluminium-hydroxide containing control	**HPV-007**; follow-on study from HPV-001 NCT00120848 (GSK)	Harper et al.,[21] Romanowski et al.[22]	2	USA, Brazil, Canada	Nov-03	Aug-07	776	15–25	5.9 years from first vaccination
Cervarix versus aluminium-hydroxide containing control	**HPV-023**/109616; follow-on study from HPV-001 and HPV-007 NCT00518336 (GSK)	De Carvalho et al.,[23] Roteli-Martins et al.,[24] Naud et al.[25]	2	Brazil	Nov-07	Jul-08	437	15–25	8.9 years from first vaccination
Cervarix versus Hepatitis A vaccine	104798 (**Konno**) NCT00316693 (GSK)	Konno et al.[26,27]	2	Japan	Apr-06	Feb-09	1040	20–25	24 month after first vaccination
Cervarix versus Hepatitis A vaccine	**PATRICIA**/HPV-008 NCT00122681 (GSK)	Paavonen et al.,[28,29] Lehtinen et al.,[30] Wheeler et al.,[31] Palmroth et al.,[32] Szarewski et al.,[33] Apter et al.,[34] Struyf et al.[35]	3	USA, Australia, Belgium, Brazil, Canada, Finland, Germany, Italy, Mexico, Philippines, Spain, Taiwan, Thailand, UK	May-04	Nov-09	18,644	15–25	Mean 43.7 months (median 47.4)
Cervarix versus Hepatitis A vaccine	Costa Rica Vaccine Trial/**CVT**/ HPV-009 NCT00128661 (NCI & GSK)	Herrero et al.,[36] Kreimer et al.,[37] Rodriguez et al.,[38] Hildesheim et al.,[39,40] Beachler et al.[41]	3	Costa Rica	Jun-04 (initiation into trial)	Dec-10 (final data collection for primary outcome)	7465	18–25	53.8 months
Cervarix versus aluminium-hydroxide containing control	**VIVIANE**/HPV-015/ 104820 NCT00294047 (GSK)	Skinner et al.,[42] Wheeler et al.[43]	3	Australia, Canada, Mexico, Netherlands, Peru, Philippines, Portugal, Russia, Singapore, Thailand, UK, USA	Feb-06	Jan-14	5747	26+	5.9 years TVC from first vaccination, 5.7 years in ATP-E group from third vaccination
Cervarix versus aluminium-hydroxide containing control	107638/**Zhu** NCT00779766 (GSK)	Zhu et al.[44,45]	3	China	Oct-08	Oct-14	6051	18–25	Mean 57 months TVC-E from first vaccination, 52 months ATP-E group from third vaccination

(continued)

Table 1. Continued.

Vaccine and control	Trial name, NCT number (and sponsor)	Research papers	Phase	Country	Start date	End date	Number of participants	Age at enrolment	Average (mean) length of follow-up
Gardasil versus aluminium hydroxyphosphate sulphate adjuvant containing control	**V501-007** NCT00365716 (Merck)	Villa et al.[46,47]	2	Brazil, Finland, Sweden, Norway, USA	May-00	May-04	552 (initial study up to three years), 241 (extension study up to five years)	16–23	Initial study up to 36 months (average not given). Extension study up to five years (results given for 226 women who completed study to 60 months, average not given)
Gardasil versus aluminium hydroxyphosphate sulphate adjuvant containing control	**FUTURE I**/ V501-013 NCT00092521 (Merck)	Garland et al.[48]	3	Australia, Austria, Brazil, Canada, Colombia, Czech Republic, Germany, Hong Kong, Italy, Mexico, New Zealand, Russia, Thailand, UK, USA (incl. Puerto Rico)	Dec-01	Jul-07	5455	16–24	Average three years from first vaccination
Gardasil versus aluminium hydroxyphosphate sulphate adjuvant containing control	**FUTURE II**/ V501-015 NCT00092534 (Merck)	Future II Study Group[49]	3	Brazil, Colombia, Denmark, Finland, Iceland, Mexico, Norway, Peru, Poland, Singapore, Sweden, UK, USA (incl. Puerto Rico)	Jun-02	Jul-07	12,167	15–26	Average three years from first vaccination
Gardasil versus aluminium hydroxyphosphate sulphate adjuvant containing control	**FUTURE III**/V501-019 NCT00090220 (Merck)	Munoz et al.[50] Castellsague et al.[51]	3	Colombia, France, Germany, Philippines, Thailand, USA, Spain	Jun-04	May-09	3819	24–45	Median 4 years (mean 3.8 years)
Gardasil versus aluminium hydroxyphosphate sulphate adjuvant containing control	**V501-027** NCT00378560 (Merck)	Yoshikawa et al.[52]	2	Japan	Jun-06	Sep-09	1021	18–26	30 months (23 months after month 7)
Gardasil versus aluminium hydroxyphosphate sulphate adjuvant containing control	**V501-041** NCT00834106 (Merck)	Wei et al.[53]	3	China	Jan-09	Sep-16	3006	20–45	Mean 6.07 years after first vaccination

Figure 2. Phase 2 and 3 randomised controlled trials on HPV vaccination efficacy.

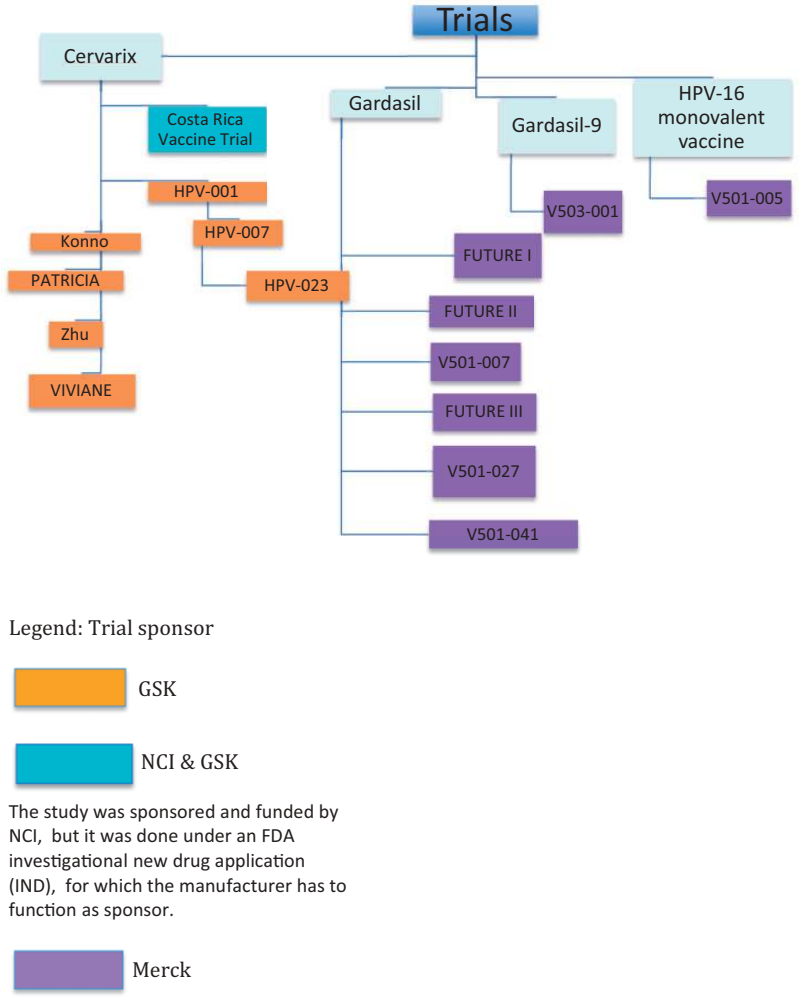


Figure 1. Five of the 12 trials (VIVIANE, V01-007, FUTURE III, V501-027, V501-041) were powered for composite outcomes that combined cervical disease and persistent HPV infection.[43,47,51–53] Four trials combined cervical disease and genital warts in the same primary outcome (FUTURE III, V501-007 and V501-027, V501-041) thereby inflating efficacy measures.[47,51–53]

CIN1+

The trial outcomes included surrogates CIN1 and CIN2, which are more common than CIN3/AIS and cervical cancer, but which often regress and are of limited clinical concern (see 'Background' section and Figure 1). For example, intervention is not recommended for CIN1. Seven trials (FUTURE I, VIVIANE, V01-007, FUTURE III, V501-027, Zhu, V501-041) included CIN1 with CIN2, CIN3 and AIS in the same primary outcome (making a composite outcome), potentially inflating vaccine efficacy as there are many more CIN1 cases than CIN2+.[43,45,47,48,51–53]

CIN2+

The incidence (rate of detection) of CIN2, CIN3 and AIS in the trials was low so although many trials showed high efficacy for the vaccine, this was in the context of very few cases of CIN2+. For example, the HPV-023 trial showed high vaccine efficacy (100% against CIN2 and CIN3 over nine years follow-up)

Table 2. Powered endpoints across trials.

Powered endpoint	Number of trials using the endpoint	Vaccine: Trials using the endpoint
HPV 16/18 incident infection	1	Cervarix: HPV-001/007/023
HPV 16/18 12-month persistent infection	1	Cervarix: CVT
HPV 16/18 6-month persistent infection	1	Cervarix: Konno
HPV 6/11/16/18 CIN1+	1	Gardasil: FUTURE I
HPV 16/18 CIN2+	5	Cervarix: CVT, PATRICIA, Zhu Gardasil: FUTURE II, V501-041
HPV 16/18 6-month persistent infection or CIN1+	2	Cervarix: VIVIANE, Zhu
HPV 16/18 6-month persistent infection or external genital lesions or CIN1+	1	Gardasil: FUTURE III
HPV 6/11/16/18 6-month persistent infection or external genital lesions or CIN1+	4	Gardasil: V501-007, FUTURE III, V501-027, V501-041

with very low incidence (only three cases, all in the control group, out of 212 participants).[25] The trials were powered for the minimum number of events needed to obtain a statistically significant result, and many trials were designed to stop once this number had been achieved. But the powered outcomes often included CIN1, which means those trials were not powered to reach a minimum number of higher-grade CIN cases. Instead of multiple short duration trials, this problem of power could have been overcome by having one large trial of longer duration in each country.

CIN3+

CIN3 is generally agreed to be the best marker for risk of cervical cancer, with rates of progression of at least 12%.[12] New evidence suggests that clinical intervention following detection on screening may be best reserved for women with CIN3.[55] Only three of the 12 trials (FUTURE I, FUTURE II, PATRICIA) reported CIN3+ or AIS in subgroups that represented the target population of women naïve to HPV (see Supplement 4).[30,49,56] The incidence of AIS in the trials is very low and only three trials (FUTURE I, FUTURE II, PATRICIA) published results for AIS alone.[30,49,56]

In these three trials, vaccine efficacy against CIN3 and AIS due to HPV 16/18 was 100% (see Supplement 4) but there were small numbers and wide confidence intervals, sometimes showing non-significance (where the confidence interval crosses zero).[49,56] Vaccine efficacy against CIN3 and AIS due to any HPV type varied substantially between the vaccines.[30,56]

What is the evidence that vaccination prevents clinically meaningful HPV infection?

It is possible to diagnose new HPV infections (incident) and ongoing infection (persistent). Studies have shown median length of HPV 16 infection to be 8.5–19.4 months and HPV 18, 7.8–12 months.[13]

The HPV001/007/023 trial used incident infection of HPV 16/18 as the primary outcome.[20,22,25] The results are not relevant to policy decision making as the current consensus reported by the WHO is that incident HPV infection is not an adequate surrogate outcome because it rarely progresses to cervical disease.[57]

There is a lack of agreement on what time period defines persistent infection,[13] and the trials may have overestimated vaccine efficacy by picking time periods that are shorter than the duration of most self-limiting infections, for example six months. In some trials, the testing interval for diagnosing six-month persistent infection was four months[36,47,52] or five months.[44,51,53]

Only one Gardasil trial, V501-041, used 12-month persistent infection as an outcome; however, the study authors only presented data for combined HPV 6/11/16/18, not for 16/18 or any oncogenic type.[53] In the Cervarix trials, 12-month HPV 16/18 persistent infection vaccine efficacy varied from

85.3 to 100% (see Supplement 5).[25,27,29,33,45] Vaccine efficacy for 12-month persistent infection by any oncogenic HPV type ranged from 10.4% to 50.1% across trials with wide confidence intervals for most trials.[25,27,29,33,45] The results were not statistically significant for the HPV-023 trial and Zhu (see Supplement 5).[25,45]

Not all trials analysed HPV types 16 and 18 separately. The incidence of HPV infection varies by HPV type.[30] HPV 18 was much less common than HPV 16. Combining their results makes the efficacy against HPV 18 appear more solid. In some trials the results for HPV 18 on its own were not statistically significant and were only significant when combined with results for HPV 16. For example, in the per-protocol population subgroup of V501-027, the six-month persistent infection or genital disease (the trial primary outcome) vaccine efficacy was 100% (59.7,100) for HPV 16, 86.0% (−8.9, 99.7) for HPV 18 and 94.5% (65.2, 99.9) for HPV 16/18.[52] In the according-to-protocol cohort for efficacy (ATP-E) subgroup of the PATRICIA trial, CIN3+ vaccine efficacy for HPV 16 was 90.2% (59.7, 98.9), HPV 18: 100% (−8.2, 100) and HPV 16/18: 91.7% (66.6, 99.1), respectively.[30] This means the vaccine may not protect as well against cervical cancer related to HPV 18. The proportion of cervical cancers related to HPV 18 ranges from 13% in South/Central America to 22% in North America.[58]

How much information is there on long-term outcomes and how long does protection last?

All trials were six or fewer years in length, apart from the extension study HPV-023 with mean follow-up of 8.9 years, (which maintained blinding and kept a control group) it only included 437 of the original 1113 participants in HPV-001.[25] The longest study of Gardasil was V501-041, which was extended from 30 to 78 months with 2601 out of the initial 3006 participants.[53]

Features of the trials may bias the findings in overestimating long-term efficacy. For example, HPV 16/18 related CIN3 presents earlier than non-vaccine type CIN3 so shorter efficacy trials will be biased in favour of finding HPV 16/18 related CIN3.[59]

Although incidence and progression of disease differ over time and by age, V501-007 combined the results of participants from the original trial with those who completed an extra two-year extension.[47] In HPV-007 and HPV-023, results for participants from the preceding trials were considered together.[22,25]

How similar were the females in the trials to the target vaccination groups?

Females in the trials are typically older than those in real-life vaccine programmes, and it is unclear whether their outcomes are similar. We do not know efficacy rates in girls aged between 9 and 13 years.

The youngest trial participants were aged 15 years and trials did not restrict recruitment to girls before sexual debut. Therefore, previous exposure to HPV is likely for some girls. Per-protocol subgroups with much fewer participants were used to analyse those with no evidence of previous HPV exposure but as shown earlier, most trials did not present data for CIN3+ outcomes in these subgroups.

Efficacy in girls aged 9–13 years has been estimated using immunobridging trials (where immune response levels are measured) rather than using clinical outcomes.[60] We do not know what level of antibody titres define a surrogate level of protection against cervical cancer or its precursors and how long protection will last (Gardasil anti-HPV 18 titres are not different from natural infection as early as 24 months after vaccination).[60] Therefore, it is possible that protection will wane by time of peak exposure when vaccinated at an earlier age.

Three trials recruited older women (FUTURE III (aged 24–45), VIVIANE (aged 26+) and V501-041 (aged 20–45)).[42,50,53] In VIVIANE a subset of up to 15% of women with a history of HPV-associated infection or disease were included (defined as two or more abnormal smears in sequence, abnormal colposcopy, or biopsy or treatment of the cervix after abnormal smear or colposcopy findings) but this means that the Total Vaccine Cohort may not reflect the proportion of women with a history of HPV-associated disease in the wider population.[42] There were then restrictions based on HPV DNA and serostatus for inclusion in the according to protocol for efficacy and total vaccine cohort for efficacy subgroups. In FUTURE III, women with a history of past or present genital warts or cervical disease were excluded; the primary tests of efficacy were in the HPV type-specific per-protocol efficacy analyses (PPE), which required women to be seronegative to relevant type on day 1 and PCR negative to that type in cervicovaginal swabs or biopsy samples, or both, from day 1 until month 7.[50] V501-041 excluded women with more than four previous sexual partners and those with a history of genital warts or 'significant cervical disease' – the study authors did not specify what this meant.[53]

Seven trials excluded women with more than four to six previous sexual partners.[20,28,46,48,52,53,61] Five excluded women with previous abnormal cervical smears[20,46,48,52,61] and an additional three excluded women with a history of previous colposcopy.[26,28,44] CVT was the only trial with no restrictions based on genital warts or cervical or sexual history.[36] These restrictions may make the vaccine appear more efficacious in the intention-to-treat (ITT) population than in the general population of women of the same age. In CVT, the efficacy in the ITT group for 12-month persistent infection with any oncogenic HPV type was 11% (95% CI 2.2, 19.5); they did not give efficacy against CIN3+ in the ITT group.[36]

There is also global variation in the epidemiology of HPV which means that the trial findings may be poorly generalisable to some settings, including Africa, so it is important to know if results differ by study region. None of the trials considering efficacy outcomes were conducted in Africa (we are only aware of a safety and immunogenicity trial in Africa[62]) despite this being the world region with by far the highest incidence of cervical cancer.[2] The Cochrane review acknowledges that 'differences in the population HPV prevalence in the trial sites, or differences in study protocols and assays used, may explain the contrast in efficacy' between Cervarix and Gardasil.[18]

What is the risk of oncogenic HPV-type substitution?

Vaccines may protect against HPV types, which are not included in the vaccine. There was some evidence of cross-protection against three high-risk HPV types (31, 33 and 45) for Cervarix (see Supplement 6).[31,36,43,45] There was cross-protection against one non-vaccine HPV type by Gardasil[31] (see Supplement 6).[63] But there was evidence of a statistically significant increased risk of HPV type 51 and 58 in the Cervarix trials, compared with the control vaccine.[31,36] It is unknown whether vaccine targeting will lead to substitution by other oncogenic types, as with pneumococcal vaccination.[64]

Methodological factors from the trials which may affect interpretation of the results

Multiple underpowered analyses

All trials undertook multiple subgroup analyses, which increase the likelihood of positive statistical findings in the absence of true effect. The subgroup definitions varied across trials, so that results cannot be compared across trials. Results were not given for all subgroups, and were not broken down by country, by study site or for each outcome. This is important given different epidemiology of HPV in different areas of the world. It may have been reported this way because incidence was low. We have included a table giving the different subgroup definitions in Supplement 7.

Problems with reporting of trial results

The trials report vaccine efficacy as the primary outcome, which shows relative risk reduction. This can over-emphasise efficacy compared with absolute risk reduction such as numbers needed to vaccinate, which is more useful for clinicians, patients and policy makers. None of the trials gave numbers needed to vaccinate. CVT is the only trial that presented results in terms of absolute risk reduction.[36,38,39] The absolute risk reduction for the PATRICIA trial for CIN3+ due to any oncogenic HPV type (see Supplement 4) (our calculation) is 0.75%, giving a number needed to vaccinate of 133.

Frequency of cervical screening

All the trials did Pap cytology at 6–12 monthly intervals. Cervical cancer screening is recommended in England every three years, between the age of 25 and 49 years.[65] Increased frequency of screening can lead to over-diagnosis and overtreatment of cytological abnormalities that would normally resolve and not be detected.[66] Increasing the frequency of testing suits early trial completion but may overestimate vaccine efficacy.

Testing methods for HPV

The tests for DNA positivity to a particular HPV type (indicating ongoing infection) and seropositivity (indicating previous infection) have limited specificity and sensitivity.[67] This is another reason HPV infection has limitations as a surrogate of cervical cancer. Only 50–70% of HPV infections result in detectable anti-HPV responses,[51] and initial seropositive status may revert to negative.[68] So subgroups of women considered naïve to HPV may have had previous exposure. Also, latent infection may be undetectable on current tests. The IARC has noted that 'it is not known how frequently this [latent infection] occurs in immunocompetent individuals, how long it lasts, what causes re-emergence into a detectable state or

what fraction of cancers arises after a period of latency'.[13] This also raises the question of whether subgroups naïve to HPV can reliably represent girls before sexual debut, and whether HPV infection is a valid surrogate outcome.

Meta-analysis of limited value due to trial heterogeneity

Differences in trial endpoints and subgroups limit the ability to compare and aggregate data from trials. This is compounded by lack of standardisation across studies for a range of measures: tests of previous HPV exposure, serological assays to detect HPV infection and sampling methods including frequency of testing.[67]

There are no agreed criteria for defining the causal HPV type for clinical lesions, and different trials used different criteria (see Supplement 8). There was no standard approach to assess efficacy against disease and infection due to HPV types not found in the vaccine, for example whether they considered non-vaccine oncogenic types or all non-vaccine HPV types (see Supplement 9). Given that Merck and GSK were involved in all the trials it is unclear why there was no consistency in methods and tests across trials.

Is ongoing research likely to resolve the uncertainties?

The focus of this paper is randomised controlled trials, but we have also looked at whether observational studies can answer some of the uncertainties, acknowledging that this is a lower level of evidence but practically the most likely source of future information in the absence of long-term randomised controlled trials. We identified 19 Phase 4, observational and non-blinded follow-up studies (including a meta-analysis of ecological studies) that are potentially relevant to the uncertainties discussed in this paper (see Supplement 10). None of these studies is ideal. Many are small, of short duration or not looking at CIN3+. One observational study (#5) showed a reduction in relative risk of CIN3 amongst those vaccinated of 0.45.[69] The PATRICIA trial follow-up (#3), the only trial planned for 20 years post-vaccination, and the Mexican FASTER trial (#18) are likely to provide more long-term efficacy data on the more clinically relevant efficacy endpoints.

The recently published observational study conducted in Scotland by Palmer et al.[70] provides new evidence on reduction of CIN3+ regardless of HPV type. The authors note the following limitations which may have inflated measures of efficacy: the study gathered data only on the first round of cervical screening at age 20 years (now changed to age 25 years in line with England) with underrepresentation of the unvaccinated group (23% screening attendance versus 51% in the vaccinated group at aged 20 or 21); and shorter follow-up time for women born in 1995 and 1996 necessarily affects the robustness of the estimate of vaccine effectiveness for younger women. In addition, the basis for the claim of herd protection is not well explained for the unvaccinated women in the 1995–1996 cohort, compared with unvaccinated women in 1988–1990. Nor do the authors consider how changes in sexual activity may have contributed to the observed decrease in CIN prevalence independent of the vaccine: between 2002 and 2014 (the latest period for which there are data) the proportion of 15-year-olds in Scotland who have ever had sex reduced, although socio-economic inequalities persist for sexual initiation and condom use.[71] Screening uptake also varies by socio-economic status.[72]

What should we do in the light of the uncertainty?

Policy

We ask policy makers to:

1. Establish national baseline epidemiological data on cancer incidence, mortality and HPV subtype prevalence to support evidence based decisions about whether the currently available vaccines are likely to be cost-effective and should be a priority.
2. Ensure that cancer surveillance and registries are in place before any vaccination programme is implemented so that changes in incidence of cervical cancer and its precursors can be studied.
3. Initiate national long-term efficacy and effectiveness studies that are free of industry funding, focus on clinically meaningful outcomes, and enrol and analyse the vaccine target populations.

Research

In the UK, cervical screening is estimated to prevent more than 80% of cervical cancers.[15] A cost-effectiveness analysis in Australia suggested that immunisation is not cost-effective in settings with established cervical screening.[73] We still do not know how many cases of cervical disease prevented by vaccination would have been detected by cervical screening. Further research is needed on whether adding vaccination where screening exists will be cost-effective.

Box 2. Recommendation for future trials to address the uncertainties.

- Vaccinate prior to onset of sexual activity and begin assessment of endpoints at age of usual cervical screening once sexually active
- Make all clinical study reports including anonymised individual patient data publicly available
- Separate trials to assess the benefit in women already exposed to HPV, without restrictions based on risk factors
- Analyse data by country and study site
- Ensure the testing interval is in line with usual cervical screening protocols
- Continue follow-up for minimum 20 years from the time of sexual debut
- Power trials for primary composite outcome CIN3/AIS/cervical cancer due to oncogenic HPV types
- Define secondary outcome of persistent infection with HPV 16/18 at a minimum of 12 months
- Use standardised testing methods for HPV detection.
- Undertake a saline placebo-controlled efficacy trial of Gardasil-9 in previously unvaccinated participants, as it is difficult to draw conclusions on efficacy and risk of harms based on the trial comparing Gardasil-9 against Gardasil.

Box 2 shows our recommendations for further research to address uncertainties. We also call for more research on HPV to be free from industry funding.

Conclusion

This review has revealed many methodological problems with the Phase 2 and 3 efficacy trials of HPV vaccination leading to uncertainty regarding understanding its efficacy.

1. *Cervical cancer* – It is uncertain whether HPV vaccination prevents cervical cancer. The trials were not designed to detect this outcome, which takes decades to develop. For most outcomes, follow-up data exist for an average of only four or five years.
2. *CIN* – There is evidence that vaccination prevents CIN1; however, this is not a clinically important outcome (no treatment is given). Trials used composite surrogate outcomes which included CIN1, but high efficacy against CIN1+ (CIN1, 2, 3 and AIS) does not necessarily mean high efficacy against CIN3+ (CIN3 and AIS), which occurred much less frequently. There are too few data to clearly conclude that HPV vaccine prevents CIN3+. CIN in general is likely to have been overdiagnosed in the trials because most carried out cervical cytology at intervals of 6–12 months rather than at the normal screening interval of 36 months. This means that the trials may have overestimated the efficacy of the vaccine as some of the lesions would have regressed spontaneously.
3. *Persistent HPV infection* – The outcomes for HPV infection are difficult to interpret. Many trials diagnosed persistent infection on the basis of frequent testing at short intervals, i.e. less than six months. This leaves uncertainty as to whether detected infections would clear or persist and lead to cervical changes. In the current Public Health England cervical screening programme, patients who are HPV positive but cytology negative are not retested for 12 months.[74]
4. *Differences between trial and real world populations* – Most of the people in the trials were older than the 9- to 13-year-olds who are typically offered vaccination. Efficacy in girls aged 9–13 years has been estimated using immunobridging trials (where immune response levels are measured) rather than using clinical efficacy outcomes.[60] We do not know what level of antibody titres protect against cervical cancer and its precursors, or how long protection will last.[60] Similarly data on the outcomes for women older than 24 years are limited, and all trials apart from the Costa Rica Vaccine Trial (CVT) had exclusions on eligibility related to sexual history or history of genital warts or cervical disease, limiting the generalisability to catch-up vaccination populations.[36] HPV epidemiology varies globally. No efficacy studies were done in Africa.
5. *Cross-protection and HPV-type substitution* – There is uncertainty about whether the vaccine will provide cross-protection against oncogenic HPV types not targeted by the vaccines. There is also a risk of substitution where a non-vaccine oncogenic HPV type fills the void left by the reduction of an HPV type targeted by the vaccines.
6. *Methodological considerations* – Many trials included multiple underpowered subgroup analyses, which increase the chance of false-positive findings. All trials except CVT reported relative rather than absolute effects, which tend to overstate efficacy, and none provided numbers needed to vaccinate.

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ANNEXURE P/12

Preliminary findings of visit to Bhadrachalam:
HPV Vaccine 'demonstration project' site in Andhra Pradesh

March 27-30, 2010

Compiled By
Sarojini N, Anjali S and Ashalata S

Centre halts HPV vaccine project
Aarti Dhar

The Hindu, 8 April 2010
New Delhi

Director-General of the Indian Council of Medical Research (ICMR) V.M. Katoch told The Hindu that he had asked the Health and Family Welfare Ministry, the State governments and the people not to go ahead with the programme. “There can be no compromise, if ethical issues have been violated by any non-governmental organization or pharmaceutical company.
In the wake of reports of violation of ethical guidelines and exploitation during the “clinical trials” of HPV (Human Papillomavirus) vaccine, meant to prevent cervical cancer among women, the Centre on Wednesday advised the State governments to suspend the vaccine programme until the issue is settled.

Vaccine programme in A.P. only after Centre's clearance
Y. Mallikarjun

The Hindu, 8 April 2010
Hyderabad

Following the controversy over the administration of the HPV (Human Papillomavirus) vaccine to tribal girls in Khammam district, the Andhra Pradesh government has decided not to allow further mass vaccination until it receives a go-ahead from the Indian Council of Medical Research (ICMR) and other competent agencies.

Cancer vaccine study in a spot
Sanchita Sharma

Hindustan Times, 11 April 2010
New Delhi

“This is not a phase -3 clinical trial but a post-licensure observational study as the vaccine-Gardasil by MSD Pharmaceutical-is approved for use in India. ICMR just evaluated the studies protocol and methodology. The state has to monitor ethical compliance but following the objection we have asked Andhra to suspend the program till a review is done”, said V.M.Katoch director general, ICMR.

Background

On July 9, 2009, the Andhra Pradesh Minister for Health and Family Welfare in association with the Indian Council of Medical Research (ICMR)[1] and PATH International[2] launched what it described as a 'demonstration project' for vaccination against cervical cancer. The vaccine, against the Human Papillomavirus (HPV)[3], was administered to 14,000 girls between the ages of 10 and 14 in three *mandals* – Bhadrachalam, Kothagudem and Thirumalayapalem – of Khammam district in Andhra Pradesh.[4] In Andhra Pradesh, the vaccine used was Gardasil, manufactured by Merck Sharpe and Dohme, the Indian subsidiary of Merck and Co. Inc., a US-based pharmaceutical company.

In a similar project, on August 13, 2009, the Gujarat government launched a two-year 'Demonstration Project for Cancer of the Cervix Vaccine' in three blocks of Vadodara District – Dabhoi, Kawant and Shinor – to administer three doses of the HPV vaccine to 16,000 girls between 10 and 14 years. The Gujarat State Minister for Health and Family Welfare claimed that this 'demonstration project' would help the Centre to examine the possibility of introducing the vaccination project across the country.[5]

Members of health networks, women's groups, organizations working on public health issues, medical professionals, human rights groups and child rights groups have raised concerns regarding the introduction of Gardasil to young girls in the country and submitted a joint memorandum to the Union Minister of Health and Family Welfare enumerating these concerns and demanding that the 'demonstration projects' be halted.[6]

There were reports of deaths of four girls, Kudumula Sarita (13 years), Sode Sayamma (14 years), Kampilla Swati (13 years) and Mundraboyina Suryalakshmi (12 years) following the administration of one to three doses of the vaccine in Bhadrachalam division, which includes Bhadrachalam, Dummugude and Kothagudem *mandal*s. We, as concerned health and women's rights' activists, felt that there was an urgent need to visit the areas where this project was being conducted, in order to understand the ground reality; in particular, to look at the nature and procedures of taking consent and providing information to the girls and their parents, and the availability of the health infrastructure required to support cancer screening and prevention.

During March 27-30, 2010, a team of women's activists visited Bhadrachalam *mandal*, one of the three *mandals* of Khammam district where the 'demonstration project' was undertaken. This report is a summary of the team's findings based on detailed interactions in the area.

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[1] The Indian Council of Medical Research (ICMR) is the apex body in India for the formulation, coordination and promotion of biomedical research.

[2] PATH (Programme for Appropriate Technology in Health) International is a non profit organization with headquarters in Seattle, Washington, USA.

[3] The Human Papilloma Virus (HPV) infects the epidermis and mucous membranes of humans, is one of the most common families of viruses and the source of a common sexually transmitted infection

[4] Press Trust of India (August 13, 2009), "Gujarat Launches Cervical Cancer Vaccine."

[5] Press Trust of India (August 13, 2009), "Gujarat Launches Cervical Cancer Vaccine."

[6] Letter to the Union Minister of Health and Family Welfare, by Member of Parliament Ms. Brinda Karat, dated March 22nd, 2010.

Part I

The 'Demonstration Project' in Khammam, AP

The *mandals* in the PATH 'demonstration project' in Khammam seem to have been selected for their diverse profiles -- Bhadrachalam (tribal), Kothagudem (urban) and Thirumalayapalem (rural). The vaccine was administered in 3 doses, at intervals of 0, 2 and 6 months, in July 2009, October 2009 and January 2010. The first dose was administered to 14,091 girls, the second to 13,930 and the third dose to 13,790 girls.[7]

The children who were part of this project were from four social groups – scheduled tribes, scheduled castes, Muslims and other backward communities. They were all from marginalised communities with poor economic background. Majority of the children vaccinated were tribal children whose parents were mainly agricultural labourers. Few girls were from families that have been displaced by the ongoing conflict in the neighbouring state Chhattisgarh.

Bhadrachalam Division – A Background

Bhadrachalam is a *mandal* in Khammam district in Andhra Pradesh. Bhadrachalam is about 130 km from the district headquarter, Khammam, and approximately 320 km east of the state capital, Hyderabad. Bhadrachalam division has a 28% of tribal population, comprising the Koyas (predominant), the Kondareddi and the Lambada tribes.[8] The main livelihood of the Koyas is agriculture and collection of local forest produce. The division is grappling with a range of problems including loss of livelihoods, resulting from large scale deforestation. The area also experiences flooding and submergence due to the overflow of the Godavari River, on whose banks Bhadrachalam is located. The situation is likely to worsen as a consequence of the Polavaram dam. Bhadrachalam division is close to the state border with Chhattisgarh and has a huge inflow of displaced (mostly) tribal families and children as a result of the ongoing conflict in parts of that state. Due to the presence of 'Operation Green Hunt' in these areas, the community in the bordering villages is under constant surveillance.

Malnutrition, malaria, dengue, diarrhoea, chikungunya and other health problems prevail in this socio-political and physical environment in the absence of accessible public health facilities. Children suffer from a range of health problems related to poverty, lack of access to nutrition and the absence of health services.

Bhadrachalam is also a popular pilgrim town with a famous temple, which draws visitors from all over the country.[9] Also located in Bhadrachalam is India's largest integrated pulping and paperboard manufacturing unit, the ITC Bhadrachalam Paperboards Ltd, the largest single location mill in India.[10]

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[7] Andhra Jyoti, March 19, 2010.
[8] http://www.aptribes.gov.in/html/basicstats.pdf, accessed on April 5, 2010
[9] The Seetha Ramachandra Swamy shrine at Bhadrachalam, the most famous temple, is situated on the left bank of the Godavari River. It is a place of pilgrimage for Hindus, considered to be one of the greatest holy shrines in South India with a very rich and unique historical background.
[10] http://www.itcpspd.com/aboutus/aboutus.html, accessed April 2, 2010.

About the Visit

In March this year, we - women's and health rights activists from Sama[11], Jan Swasthya Abhiyan[12] and Anthra[13], who have been engaging on this issue since last year visited Bhadrachalam, one of the *mandals* in Khammam district where the vaccine was being administered, after the deaths of four girls following vaccination were reported by the media.

We visited Residential Schools and Hostel for tribal girls and Residential Bridge Course (RBC) school. We spoke to wardens, teachers and assistants of four residential schools in the *mandal* and girls who have been administered the HPV vaccine as well as those who were not part of the vaccine programme. Our interactions with the students and teachers / wardens were carried out after explaining the purpose of our visit and obtaining their permission.

We interacted with the parents of Kudumula Sarita, who died in January 2010, following the third dose of the vaccine. Interviews also took place with Korna Chilakamma, from the village of Sode Sayamma, who died in the previous year (2009). We also had discussions with members of local *adivasi sanghatans* and activists including Kunja Srinivas and Midiyam Ramanamma of Adarsha Women's Society[14], Marlapati Renuka and other members of All India Democratic Women's Association (AIDWA)[15]. The local activists and members of AIDWA accompanied us on visits to the local schools from Bhadrachalam, facilitated our interactions with parents of the girls who were vaccinated and with the parents of Sarita. The interactions were carried out in the local languages, i.e. Telugu and Koya (local dialect, with the help of the local activists).

We also visited two PHCs at Nellipaka and Lakshmipuram. The medical officer at the Nellipaka PHC, one of the health centres that was implementing the 'demonstration project', was not willing to speak to us without permission from higher authorities. Due to paucity of time, we were unable to interact with the district immunization officer, or travel to the other *mandals*. However, we had discussions with the health staff from the PHC in the field area.

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[11] Sama- Resource Group for Women and Health is a Delhi based organization, which has been working on various issues of women's health and rights in India. Sama has been campaigning against the violations on women's health rights through the misuse of reproductive and medical technologies and unethical clinical trials.

[12] The Jan Swasthya Abhiyan is the Indian circle of the People's Health Movement, a worldwide network of people's organizations, civil society organizations, NGOs, social activists, health professionals, academics and researchers working to establish health and equitable development as top priorities through comprehensive primary health care and action on the social determinants of health.

[13] Anthra is a Hyderabad based organization led by Women Veterinary Scientists that works on issues concerning people's livelihoods, livestock, food sovereignty and environmental justice.

[14] Adarsha Women's Society in Bhadrachalam *mandal* has taken up several campaigns in the area for adivasi rights, women's rights, forest rights, food security, education, etc.

[15] The All India Democratic Women's Association (AIDWA) is an independent left oriented women's organization committed to achieving democracy, equality and women's emancipation.

Part II

Key Findings

We visited two residential schools for tribal girls (here after referred as *Ashram Paathshalas*) and one hostel for tribal girls - namely - the *Andhra Pradesh Girijana Sankshema Balikala Gurukula Kalashala (APTWRJC[16], Bhadrachalam town), Girijana Balikala Ashrama Paathshala (High School for girls in Ramchandrapuram, Bhadrachalam division), Prabhutva Girijana Balikala Vasati Griham (ST Balika Hostel, Bhadrachalam town)*. We also visited a Residential Bridge Course school (RBC)[17]. The Ashram Paathshalas, *ST Balika Hostel* and RBC are run by the Integrated Tribal Development Agency (ITDA), Andhra Pradesh.

We also visited another RBC school located in a red cross building in Chintur Mandal, very close to the banks of the river Shabari. The villages in this area are submerged during the monsoon when the river floods. Because of this, the school is housed away from the village, slightly uphill. On asking some of the staff at this school, we learnt that none of the children were vaccinated in this drive as the school did not fall under the three selected PHCs. However, they also told us that a few months earlier, an ANM had visited the school and taken the list of birthdates from the school.

The ST Balika Hostel[18] and the APTWRJC (with classes up to Class X and a junior college), we were informed, had a total strength of about 500 and 1,000 girls respectively. The Girijana Ashram High School (Ramchandrapuram)[19] had a total strength of about 500 girls.

The children (both boys and girls) in the RBC school visited, are originally from Chhattisgarh, displaced by the ongoing conflict in the neighbouring state. Some of them have witnessed violence; lost either one or both parents, siblings in this conflict. They belong to the Chhattisgarhi Koya tribe, who speak in the Koya dialect and know little Telugu. Initially, they are taught Telugu to prepare them for formal school education and to understand the school curricula which is in Telugu language.

The RBC is a residential school where the children study, live and sleep within the same space, which is quite cramped. We came to know that, under this programme, a fund of Rs. 14 per child per day is given to the school. Each child is given two pairs of clothes, soap and one bottle of hair oil. Most of these children are malnourished and suffer from skin diseases.

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[16] Andhra Pradesh Tribal Welfare Residential Junior College.

[17] RBC schools have been set up under the District Primary Education Programme for school dropouts in the 9-14 year age group. It is a programme to reintegrate the students into the formal ITDA schools, according to age and eligibility.

[18] The hostel seemed very organised and well run. A register of the hostel's rations (including food grains, clothes for the girls, furniture, soaps and sanitary napkins), the daily menu, lists of ex-students etc. was displayed on the boards in the corridors. Since it was a Sunday, many of the girls were busy washing their clothes and attending to other such personal tasks. The welfare officer told us that a full time health volunteer, Aarogya Deepika, stays at the school. However, on the day of the visit, she was not there.

[19] The warden here said that the dropout rate was quite high, especially before the English and Maths exams. Some girls even try to climb the compound wall and run away from the hostel, and return after the exams. According to her, many students return afterwards because their lives at home are very tough and they do not get enough food to eat. She said that at least in school they were getting wholesome meals three times a day, with all the necessary nutrition. They were also given four pairs of clothes, sanitary napkins, soap and hair oil. She mentioned that for the

About 300 girls at ST Balika Hostel and 400 girls from APTWRJC, all from classes six to nine were vaccinated. On the days of the vaccination, 'camps' were conducted in the corridors and campus of the school and hostel. The welfare officer of the ST Balika Hostel informed us that she was not around at the time of the first vaccination and the teacher in charge had given consent for it. At the Ashram Paathshala in Ramchandrapuram, the warden informed us that many girls had got the vaccine, but she could not specify the number.

At the RBC, we learned that initially an ANM had come to the school and asked for a list of birth dates of all the girls. Five girls were selected for vaccination and were taken to the nearby 'camp' set up in the local school by the ANM and the teacher. It is important to note that a majority of these children do not have any official identity papers or birth certificates. The birth dates maintained in the records are generally speculative, and not accurate. We were able to speak to four of the vaccinated girls. The fifth girl had dropped out of school as she had moved to another place and not completed all three doses of the vaccine. The girls appeared frail, underweight, anaemic and had not started menstruation.

We also interacted with two girls at the local AIDWA office, who were day scholars at Nannapaneni Zila Parishad High School and their mothers. These girls had been administered the vaccine and were suffering from adverse effects.

Our interactions revealed the following:

Check up and screening for contraindications

Before the first dose, a physical check up of the girls was carried out and their weight and height measured. However, for the subsequent doses they were not weighed. After the vaccination, the girls were asked to sit down for 10 minutes, and then sent to class. Many girls could not articulate whether they were asked for any contraindications such as illness, fits, fever, etc.

One of the girls (Zila Parishad School) said that her classmate, who had asthma, was given the vaccine after the nurse spoke to her parents. One girl, who had malaria at the time of the first dose, was not given the injection and after she recovered, her parents came and insisted that she be given the vaccine.

Information

Most of the girls in the two Ashram Paathshalas and ST Balika Hostel reported that they were told that the vaccine would prevent *garbasanchi* (uterine) cancer from which many women die. The girls did not know what 'uterus' or 'cervix' meant and where they were located in the body. At APTWRJC, after the first dose, the girls were told that it was compulsory for them to take the following two doses. Wherever information was provided to the girls and their parents/wardens, they were told that the vaccine would provide life-long protection, has no side-effects and will not affect future fertility of the young girls.

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last two months, the supply of sanitary napkins had stopped, regarding which they were going to appeal to the ITDA project officer.

The parents of the girls in these Ashram Paathshalas were not even informed that their daughters were being vaccinated. At the RBC, the girls articulated that they were told that the vaccine would prevent fever. On further probing, they said that the vaccine would prevent cancer, although, again, they had no understanding of cancer or the uterus/cervix.

In the schools and the hostel, the girls were given the HPV Immunization Card, which was in English and which neither the girls, nor their parents were able to read. Some girls in the hostel had picked up information brochures (in Telugu) as well, which had not been otherwise handed out to all. Amongst those who picked up these brochures, very few had actually read them. The girls at the RBC were not given any material other than the HPV immunization card, which was in English.

One mother we spoke to said, "Since it was a vaccine being given by the government, we all trusted it blindly and considered it reliable, like any other vaccine that was given as part of the immunization programme". The parents told us that many of them who had heard about the vaccination project had brought their daughters to the camps organized for the vaccination. "We were all told that if your child takes this injection, she will not get uterine cancer and moreover the government is giving it free of cost".

HPV Immunization Card

On the card the project is called "HPV Vaccination Campaign by the Department of Health and Family Welfare, Government of Andhra Pradesh". This 'HPV Immunisation Card' contains the logos of the National Rural Health Mission (NRHM) and PATH, along with the contact details of the District Immunization Officer (DIO) and a toll free number. The card also contains the girls' 'Unique ID Number' along with her name, date of birth and the name of either her father or her mother. There was provision for the name of the school, ashram or hostel and the class. The card also has the provision to record the name of the village, the subcentre and PHC to which the village was affiliated, and the name of the Block.

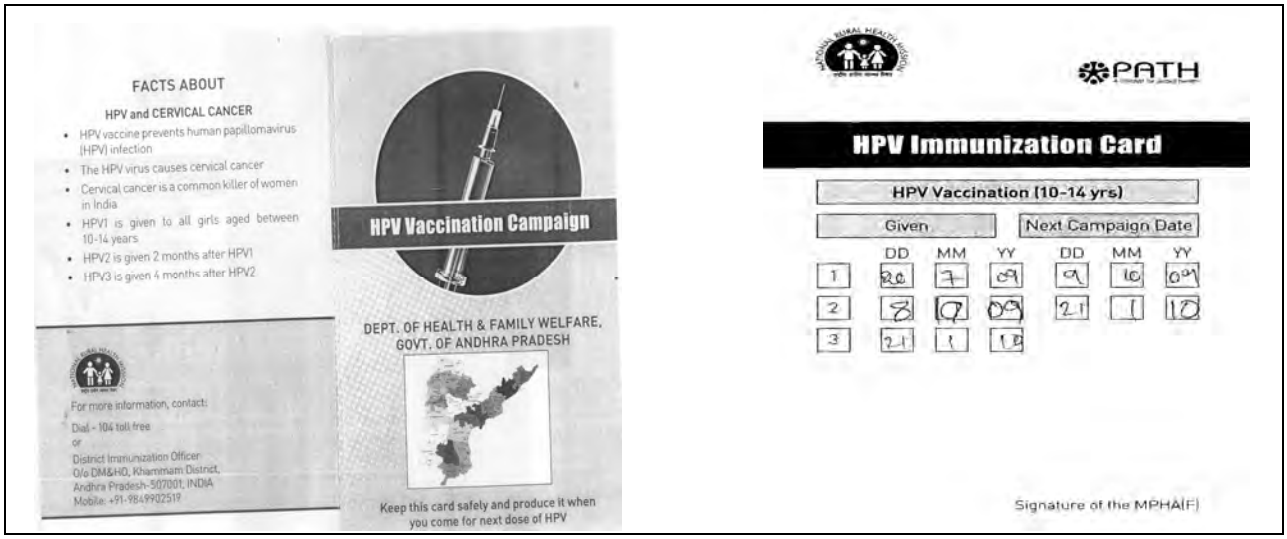
The card is to be signed by the Multi Purpose Health Attendant Female (MPHAF)**.** The back of the card contains **'**Facts about HPV and Cervical Cancer'. The 'facts' mentioned were:

- HPV vaccine prevents HPV infection
- The HPV virus causes cervical cancer
- Cervical cancer is a common killer of women in India
- HPV1 is given to all girls aged between 10-14 years
- HPV2 is given 2 months after HPV1
- HPV3 is given 4 months after HPV2

Space was allocated to record the scheduled dates for administration of subsequent doses along with the actual dates of vaccination.

Comments: *There was no provision for the girl's address in the card.*
In many of the cards, although the date for the first dose was mentioned, the rest of the boxes were left vacant.
Some of the cards did not have the signatures of the MPHAF.
The card is in English, raising issues related to the transaction of information.

The *assistant* at the RBC said that she was also told that the vaccine would 'prevent uterine cancer' and that this was a very expensive medicine worth Rs. 9,000 that they were giving free to the children; it would be such a loss for the children if the parents don't avail of this opportunity. She also got her daughter vaccinated at the camp. She was not asked to sign anything, although her daughter was given the HPV immunization card.



The HPV Vaccination Card

Consent

The girls from the two Ashram Paathshalas, hostel and RBC school with whom we had interactions, told us that their parents were not informed about the form and their signatures were not taken.

The girls at the Zila Parishad School were given forms to be signed by their parents. The girls showed us the form titled 'Consent form' which was in Telugu. They said that only 20 children from their classes brought back signed forms and on the day of the vaccination, only those 20 girls were called. They also said that there were few girls who didn't take the second dose. For girls, who were absent on the day of the second dose, the ANMs went to their houses to ask them to come for vaccination.

In the two schools and hostel, the process of consent was unclear. In ST Balika Hostel, the hostel welfare officer said that the teacher in charge at the time had given consent for vaccination of around 300 girls as she was not around before the first dose. In the APTWRJC, the teachers with whom we spoke said it was probably the hostel warden who gave the consent for the (approximately) 300-400 girls. At the RBC, the teachers told us that they had been informed about the vaccination by the ANM, following which, they and the ANMs accompanied the girls to the 'camp'.

A copy of the roughly translated consent form is given in the box below. (Please refer to the Key Findings section for concerns):

CONSENT FOR PARTICIPATION IN
CERVICAL CANCER VACCINATION
PROGRAMME, KHAMMAM DT.
ANDHRA PRADESH.[20]

The licensed vaccine Gardasil is being used in India to protect adolescent girls from being affected by the most common varieties of the virus that causes cervical cancer. This research project has been taken up to search for the best ways to provide the vaccine to adolescent girls in Khammam district. Since your daughter is suitable to take the vaccine, we request you to allow her to participate in this cervical cancer vaccination programme.

ABOUT PREVENTION OF CERVICAL CANCER:

- Cervical cancer is the main cause of death in women worldwide. Of all the cancers that affect women in India, this is the second largest cancer affecting women. Cervical cancer causes death in women more than any other cancer.
- Cervical cancer is caused by the Human Papilloma Virus (HPV). 70% of the cervical cancer cases are caused by two HPV types (16 & 18).
- To protect from cervical cancer caused by HPV type 16 and 18, safe and effective vaccines are now available. This vaccine has to be administered in three doses within six months. The best results are obtained by administering to adolescent girls. This vaccine is being used in many countries worldwide.
- HPV vaccine has been proven to be safe. Across the globe, the girls who had been administered the vaccine mentioned some side effects, research on which proved that the side effects had no relationship with the vaccine.*

INFORMATION ABOUT THE HPV VACCINATION PROGRAMME:

1. This vaccine is injected only in the upper part of the hand. Like in any other vaccine, this vaccine also causes pain, redness and swelling of the area where it has been injected. The patient may suffer from mild fever, 'swimming head' / dizziness, stomach churning / pain. These mild symptoms will subside in two to three days. If there is mild fever, it is advisable to take paracetamol. To ensure that your daughter is safe, health workers will keep her under observation for 15 minutes after she has been injected.
2. Like in the case of any other vaccine, it is possible that your daughter may suffer from rare side effects such as allergic reactions or unconsciousness. During administration of the vaccine to your daughter, if there are any severe side effects, we have trained health workers available with medicines.
3. For administration of the HPV vaccine to your daughter, no money will be collected from you.
4. The decision to give the HPV vaccine to your daughter is voluntary. If you are not willing to participate you will not lose any benefits that you are entitled to; you will not be fined.
5. If you have any additional questions on HPV vaccination, please contact:

[20] The original form in Telugu was provided by a parent and has been roughly translated into English for the purpose of this report.

Name: Dr. B. Jayakumar,
Designation: District Immunization Officer, HPV Vaccine Project Co-researcher.
Telephone: 08742-258698, Mobile: 09849902519.

Name: Dr. Satish B Kaipilyavar,
Designation: PATH Andhra Pradesh Co-ordinator and Co-researcher, HPV Vaccine Project.
Telephone: 040-24600192, Mobile: 09848019694.

* PATH Publication, Outlook, Volume 23, No.1, June 2007,
http://www.who.int/wer/2009/wer8405.pdf

Consent Form

I have read the information given in this consent form or it has been read out to me. I hereby agree to allow my daughter to take three doses of the HPV vaccine.

Daughter's name (Please Write):
Father's / Mother's / Guardian's name (Please Write)
1.Mother's / Father's / Guardian's signature:
Date:
OR
Mother's / Father's / Guardian's thumb impression
Date:

1. Name of Researcher (Please write):
Designation:
2. Signature of Researcher:
Date:
Mobile number:

Fill the following if witness is required:

If the mother, father, or guardian cannot read this consent form, this will be read out to him/her by a third person and the consent process will be explained in the presence of the unprejudiced undersigned witness.

I, the mother / father / guardian declare that the information is correctly read out to me and that I have understood the matter. I, the mother / father / guardian voluntarily agree to the administration of the HPV vaccine to my daughter.

Name of Witness (Please write):

Signature of Witness:

Date:

The consent form in Telugu is given below.

సర్వైకల్ క్యాన్సర్ వ్యాక్సినేషన్ కార్యక్రమంలో పాల్గొనుటకు సమ్మతి, ఖమ్మం జిల్లా, ఆంధ్రప్రదేశ్.

సర్వైకల్ క్యాన్సర్ కలిగించే అత్యంత సాధారణరకాల వైరస్ బారినుండి యుక్తవయస్కులైన బాలికలను రక్షించడం కోసం భారతదేశంలో ఉపయోగించే లైసెన్సు పొందిన వ్యాక్సిన్ గర్డాసిల్®. ఇది ఖమ్మం జిల్లాలో యుక్తవయస్కులైన బాలికలకు ఈ వ్యాక్సిన్ అంధజేయడంలో అత్యుత్తమ మార్గాలను అన్వేషించడం కోసం చేపట్టిన పరిశోధన ప్రాజెక్టు. ఈ వ్యాక్సిన్ పొందే యోగ్యత కలిగిన కుమార్తె మీకు ఉన్నందువల్ల సర్వైకల్ క్యాన్సర్ వ్యాక్సినేషన్ కార్యక్రమంలో ఆమె పాల్గొనడానికి సమ్మతించవలసిందిగా మిమ్మల్ని కోరుతున్నాము.

సర్వైకల్ క్యాన్సర్ నివారించే వ్యాక్సిన్ గురించి.

- సర్వైకల్ క్యాన్సర్ ప్రపంచవ్యాప్తంగా మహిళల మరణాలకు ప్రధానకారణం. భారతదేశంలో మహిళలకు ఎక్కువగా సోకే క్యాన్సర్లలో సర్వైకల్ క్యాన్సర్ రెండవది, మిగతా అన్ని రకాలు క్యాన్సర్ల కన్నా దీనివల్ల మహిళలు ఎక్కువగా మరణిస్తున్నారు.
- సర్వైకల్ క్యాన్సర్ హ్యూమన్ పాపిలోమావైరస్(HPV)వల్ల కలుగుతుంది. 70% సర్వైకల్ క్యాన్సర్ కేసులు రెండురకాల HPV (16 & 18) వల్ల కలుగుతున్నాయి.
- HPV రకాలు 16 మరియు 18 వలన కలిగే సర్వైకల్ క్యాన్సర్ బారినుండి రక్షించడానికి ఇప్పుడు సురక్షితమైన, అత్యంత ప్రభావపూరితమైన వ్యాక్సిన్లు లభిస్తున్నాయి. ఈ వ్యాక్సిన్లను ఆరు నెలలకాలంలో మూడు డోసులలో ఇవ్వవలసి ఉంటుంది. యుక్తవయసు బాలికలకు ఈ వ్యాక్సిన్లు ఇచ్చినట్లయితే అత్యుత్తమ ఫలితం లభిస్తుంది. ఈ వ్యాక్సిన్లను ప్రపంచమంతటా అనేక దేశాలలో వాడుతున్నారు.
- HPV వ్యాక్సిన్ సురక్షితమైనదని రుజువైంది. ప్రపంచవ్యాప్తంగా ఈ వ్యాక్సిన్ స్వీకరించిన బాలికలు పేర్కొన్నటువంటి తీవ్రమైన సైడ్ ఎఫెక్టులపై పరిశోధనలు జరిపి వ్యాక్సిన్‌కు వాటితో సంబంధం లేదని నిర్ధారించారు.*

HPV వ్యాక్సినేషన్ కార్యక్రమం గురించి సమాచారం.

1. ఈ వ్యాక్సిన్ చేతిపై భాగంలో ఇవ్వడం వలన అప్పుడప్పుడు [illegible] HPV వల్ల కూడా సంభవించే ఇన్ఫెక్షన్ కోసం కాపు, ఎర్రదనం లేదా వాపు వంటివి కలుగవచ్చు. స్వల్పంగా జ్వరం రావడం లేదా పడిపోతున్నట్లు స్వల్పంగా అనిపించడం, తలతిరుగుడు లేదా కడుపులో త్రిప్పడం సంభవించవచ్చు. ఈ స్వల్ప లక్షణాలు, రెండు మూడు రోజులలో తగ్గిపోతాయి. కొద్దిగా జ్వరం ఉన్నట్లయితే పారాసిటమాల్ మాత్రలు ఇవ్వవచ్చు. మీ కుమార్తె క్షేమంగా ఉందని నిర్ధారించుకోవడం కోసం టీకా ఇచ్చిన తరువాత 15 నిమిషాల పాటు ఆరోగ్య కార్యకర్తలు ఆమెను గమనిస్తారు.
2. ఇతర టీకాల వలే మీ కుమార్తె ఎలర్జిక్ రియాక్షన్లు లేదా స్పృహా తప్పడంవంటి అరుదైన తీవ్ర సైడ్ ఎఫెక్టులకు గురికావచ్చు. మీ కుమార్తెకు టీకా ఇచ్చే సమయంలో ఎటువంటి తీవ్రమైన సైడ్ ఎఫెక్టునైనా చికిత్స చేయడానికి శిక్షణపొందిన ఆరోగ్యకార్యకర్తలు, మందులు సిద్ధంగా ఉంటాయి.
3. HPV వ్యాక్సిన్‌ను మీ కుమార్తెకు ఇచ్చినందుకు మీ నుండి ఎటువంటి రుసుము వసూలు చేయరు.
4. మీ కుమార్తె HPV వ్యాక్సిన్ ఇప్పించాలనే నిర్ణయం స్వచ్ఛందమైనది. పాల్గొనడానికి నిరాకరించడం వల్ల మీకు లభించవలసిన ప్రయోజనాలను నష్టపోవడంగానీ, మీపై జరిమానా విధించడం గానీ జరగదు.
5. HPV వ్యాక్సినేషన్ గురించి మీకు ఏవైన అదనపు ప్రశ్నలు ఉన్నట్లయితే దయచేసి సంప్రదించండి:

పేరు: డా.బి జయకుమార్.
శీర్షిక: జిల్లా రోగనిరోధక టీకాకరణ అధికారి, HPV వ్యాక్సిన్ ప్రాజెక్టు సహ పరిశోధకుడు.
టెలీఫోన్ నెంబర్: 08742-258698, మొబైల్ 09849902519

పేరు: డా. సతీష్ బిత్తెపిల్యావర్
శీర్షిక: పాథ్ ఆంధ్రప్రదేశ్ సమన్వయకర్త, సహ పరిశోధకుడు, HPV వ్యాక్సిన్ ప్రాజెక్టు.
టెలీఫోన్ నెంబర్: 040-24600192, మొబైల్: 09848019694

* పాథ్ వల్లికేషన్, అవుట్ లుక్, వాల్యూమ్ 23 నెంబర్ 1, జూన్ 2007, http://www.who.int/wer/2009/wer8405.pdf

Visit to Primary Health Centre (PHC)

We visited two PHCs – one at Nellipaka and the other at Lakshmipuram. The PHC at Nellipaka was one of the main centres for the vaccination. It was from this PHC that the ANMs collected the vaccine, which was administered at different schools, hostels and at other subcentres in the area. Almost 2387 vaccines were distributed from this PHC.[21] However, when we reached this PHC, there was no sign of this project. While the locals confirmed that there had been banners at the camps in the schools and at the PHC on the day of the vaccination, not a single banner was there when we visited. It was late afternoon by the time we arrived and no one was available at either of these PHCs.

Interaction with PHC Staff

We interacted with the health staff in the field area. They informed us that initially a survey was done at all the schools in the area to identify children in the age group of 10 – 14 years. They told us that this survey was done on the basis of a Government Order (GO), issued by the District Immunization Officer (DIO) and the actual dates of the vaccination were given in the Medical Officer's action plan. Around the same time, a team of two people – the District Immunization Officer (DIO) and a representative from the PATH office in Hyderabad – had come to the PHC to train the health staff to administer the vaccine. The orientation was on the HPV vaccine, how it prevents cervical cancer, the dosage, the age group, etc. The health staff was also asked to do a basic physical check up and to record the height and weight of the girls. They were informed that this was a pilot project for the HPV vaccination, and were given tally sheets to maintain records of the vaccination. They were told not to administer the vaccine to girls who were diagnosed with any disease, or had a history of fits or were ill with malaria.

After this, the health staff was sent to different schools and hostels to administer the vaccine, where camps were set up with banners for the project. The three doses of the vaccine were administered in July 2009, October 2009 and January 2010. The project was launched by the Deputy Director, ITDA, at the APTWRJC. The vaccine was administered through a camp approach as the staff and the infrastructure in the PHC was not adequate. The health staff was also asked to follow up on the girls who did not come back for subsequent doses, and to ensure that all three doses were taken. During the training, they were told that only girls in the age group of 10 – 14 years should be given the vaccine because they were not sexually active yet.

The health staff mentioned that although at the time of the first dose the numbers were a little low, following the first dose, the demand for the vaccine went up quite a bit. Many parents came and insisted that their daughters also be given the vaccine. One hostel warden, who had initially opposed the vaccine, later came back and asked them to administer it in her hostel, because she had "been convinced" about the "good effects of the vaccine". The vaccine had been stopped for the time being since there was no more stock, but plans were on to restart vaccination in the other schools in June 2010.

[21] Information gathered by activists from Nellipaka PHC.

Sarita's Story: Meeting with Kudumula Venkatamma and Nageshwara Rao, parents of Sarita (13 years)

The members of AIDWA facilitated an interaction with Venkatamma and Nageshwara Rao[22], parents of Kudumula Sarita, who died in January 2010. They belong to Anjipakka village in Dummugudem *mandal*. The parents shared with us that the death of their daughter, Sarita, happened following the vaccination. They told us that their daughter did not die by consuming pesticide. Initially, they did not know about the HPV vaccine and were not informed by the warden or by the health staff before its administration. The interaction is documented here in their words:

After the first dose of the vaccine, our daughter Sarita did not have any reaction. She fainted upon receiving the second dose in school. This was in the afternoon. Nobody informed us. She was taken to the hospital. That evening, some villagers who visited the school told us what had happened. When we went to see her the next morning, we asked her how she was, and she said she was okay. She said that she had got an injection and after the injection she had felt dizzy and fainted. She was then shown to a doctor. We asked her if she wanted to see another doctor, but she refused saying that she had exams coming up.

When Sarita came home for Sankranti, she complained of constant headaches, stomach pains and mood swings. She used to also tap the top of her head with her hand. On January 21, Sarita did not get out of bed in the morning. Her eyes were red. As we were going to work, we asked her what the matter was and she replied that her head was spinning.

Later that day, she went to her uncle's place in the neighbourhood and fell flat at the threshold of his house. She had a fit and began to thrash her arms and legs around. Her cousin sister saw her and came running to the field to get us. She said, "Pinni (aunty), chelli (sister) has fallen down and her eyes are not stable. She is not speaking." We rushed her to the PHC, where they asked us to take her to the Bhadrachalam hospital. By the time we reached there, she had died. Since we had brought her in a 1-0-8 ambulance, we were informed that a post mortem was required. The hospital in Bhadrachalam kept the body for a day. We brought our daughter back and cremated her the next day.

Our child was active and happy. We lost our child, and we know the pain and the agony of that loss. We don't want any other child to die. We don't want any other parent to suffer. Care should be taken for other children who received the vaccination. We want the government to take immediate action. This is our only appeal. This is why we are speaking out.

Interaction with members of AIDWA members and *adivasi sanghatana*

The group shared that the Bhadrachalam area has a high incidence of malaria and dengue and many children here are undernourished. Ironically, the government is spending money on expensive vaccines instead of focusing on these epidemics and illnesses. Further, people usually trust vaccines administered by the government believing them to be good. In this particular context, people were told that they were "fortunate to be getting this vaccine for

[22] The names and other details about the parents are documented here with their permission.

free, which would be out of the reach of their daughters after the 'demonstration project'. Moreover, all of us were informed that if the girls take this injection, they will not get *garbasanchi* (uterine) cancer. Since cancer is a dreaded disease all of us felt that this injection will do good for our daughters. However, once they started complaining of headaches, stomach aches, we realised that we were not given complete information".

Korna Chilakamma from Yerragattu village, also the village of Sode Sayi (Sayamma) Kumari, who died in 2009, shared about Sayamma, who died within two weeks of the first dose of the HPV vaccine, administered in July 2009. She continued to complain of stomach pain and constant headache after the vaccination. In August, Sayamma complained of severe stomach pain, and her uncle took her to a local doctor on his motorcycle. The doctor advised him to take her to a bigger hospital in Bhadrachalam town. However, within two hours of reaching the hospital, Sayamma passed away. Sayamma's parents had no information about the HPV vaccination that was administered to their daughter. The local authorities attributed her death to "suicide by consuming pesticide", with the rationale that Sayamma was already depressed by the recent death of her sister. According to Chilakamma, the parents believed that their daughter had not consumed poison and that it was not a suicide.

Side effects

The warden at ST Balika Hostel said that all the girls were fine after the vaccination and none of them had any side effects. Many girls, with whom we interacted, said that they did not have any side effects. However, some of them told us about some health problems that they were experiencing following the vaccination. One girl (at ST Balika Hostel) said that she had started having severe stomach ache immediately after the second dose. Despite this, she was given the third dose and told not to worry. During one holiday, her parents took her to the local healer in their village, where she was given some herbal potion. However, she continued to be in pain and felt weak, even as we interacted with her. She said one of her friends (who was absent) was also suffering from headaches, giddiness and stomach pain.

Some of the girls also mentioned that they had started menstruating soon after the vaccination. A few complained of heavy bleeding and menstrual cramps. Some also said that they had experienced pain in the injection site, which remained for a few days after the vaccination.

Some girls in the Ashram Paathshalas reported that that they had developed headaches immediately after the first dose of the vaccine. They said that many of their friends, who were not present during the interaction, had also had headaches and stomach aches. Some of them still complained of such aches and pains along with dizziness.

One of the girls from the Zila Parishad school mentioned that soon after the first dose, she developed such severe stomach pain that she began to cry. She also said that because there were so many girls, the ANM was administering the injections very roughly, which made it even more painful. Another girl mentioned that she too had developed a bad headache on the day that the first dose was administered, and after the subsequent two doses, she developed a rash and itchiness. One of the girls told us that since the vaccination, she feels very moody and irritated and sometimes prefers to be by herself. She also shared that since the vaccination, she feels bothered when there is a lot of noise in the class.

KEY QUESTIONS and CONCERNS

1. Demonstration Project, Clinical Trial or Post Marketing Surveillance (PMS)?

- The nature of the project is not clear - is this a research, a clinical trial (and which phase), PMS, 'demonstration project' or an observational study? If it is a 'demonstration project', as described by the government and PATH, it is not clear what is it they were seeking to demonstrate? What were the objectives of the 'demonstration project'? However, the 'consent form' states that it is a research, a '*Parishodhana*'.

- There is lack of clarity about the nature of the project, which raises serious concerns about the nature of selection of area and children, lack of precautions, lack of full and complete information, the lack of monitoring, the process of obtaining consent, and follow up of those who have been administered with the vaccine - which directly concerns the safety of the children.

- Since there is ambiguity regarding the nomenclature, it is important to know on what grounds the Drug Regultory authorities have approved this vaccine 'demonstration project'.

2. Selection: Vulnerable groups

- The project is being conducted on minor girls from the poorest and most marginalised sections of society. The girls who were part of this project were from four social groups – scheduled tribes, scheduled castes, Muslims, children from internally displaced communities and other backward communities. Majority of the children vaccinated were tribal children whose parents were mainly agricultural labourers.
  The vulnerability of this already poor and marginalised tribal community is compounded because of the lack of access to health care, lack of access to information, absence of mechanisms for reporting adverse effects.

- Majority of the girls who were vaccinated in Bhadrachalam division were also residing in *ashram paathshalas*. The selection of girls mostly from *ashram paathshalas* is questionable, given the obvious fact that parents, living separately from their children, cannot monitor and respond to any adverse developments in their children's health. By choosing girls living in residential schools and hostels, the authorities have also dodged the provision of parental consent. This needs to be justified, as according to the ICMR guidelines, selection of participants with 'reduced autonomy' like students (more so in case of residential students), needs to be explained.

  Adequate justification is required for the involvement of participants such as prisoners, students, subordinates…who have reduced autonomy as research participants, since their consent may be under duress or various other compelling reasons. [ICMR 2006 Ethical Guidelines for Biomedical Research on Human Participants, Selection of Special Groups as Research Participants, Pg, 29]

- The 'researchers' thus successfully zeroed in on a group of children who were socio-economically weak, malnourished, with no or little access to health care facilities, did not live with their parents and did not understand the language in which information

was provided (English, and Telugu in some cases). The 'target group' of this vaccination project was chosen to be those who could not question the procedure or the motives of the 'project'.

- This raises suspicion about the motivation behind such a targeting, especially of tribal children. Why should state institutions like hostels and schools be used for such a 'demonstration' project?
- However, the Ethical Guidelines for Biomedical Research on Human Subjects by the ICMR state that *persons who are economically or socially disadvantaged should not be used to benefit those who are better off than them*.[23]

3. Dubious Nature of Information and Consent

The interactions with the wardens, teachers and students spoken to did not at all imply that they understood the vaccination initiative as a study. They believed it to be a public immunization program and had no reasons to believe that they were part of a research. To them, the government was providing an expensive vaccine free of cost that would prevent them from having 'uterine cancer' or 'cervical cancer'. In fact, they were not made aware that they had a choice regarding participation in the study and that the administration depended on their and their parents' consent. This kind of implementation goes against the very spirit of the concept of informed consent.

a. An incomprehensible HPV immunisation card

- The HPV immunisation card in English was given to all the girls after administration of the first dose of the vaccine to remind them about the vaccination schedule – second and third doses. However neither the girls, nor their parents, were familiar with the language, undermining the process of dissemination of necessary information.

- The HPV immunization card carries the logo of National Rural Health Mission (NRHM) and PATH. This raises serious questions about the role of NRHM in this programme. None of the NRHM documents mention this particular 'demonstration project'.

- There seems to be a casual attitude amongst the administrators of the vaccine with regard to the maintenance of records. In some instances, the dates for the follow up vaccines were not marked clearly. Some of the HPV immunization cards given to the girls did not have signatures of the health staff.

b. Consent form - just a 'formality'

- The wardens of the residential schools and hostels, which were selected for the 'demonstration project', were asked to provide consent or permission for vaccination. Can the wardens be considered legal guardians to provide consent? How can a warden, whether a legal guardian or not, be allowed to sign or provide consent for hundreds of children without consulting with the parents, who are the natural guardians.

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[23] Indian Council of Medical Research, 2006, Ethical Guidelines for Biomedical Research on Human Participants, Section IV *Selection of Special Groups as Research Participants,* Pg. 28.

- On the basis of the interactions, it appears that the 'consent form' (*Angikaara Patram*) was used mainly in the case of non-residential schools. The children were asked to get the consent form signed by the parents, which raises concerns about violation of the process of obtaining consent. Such a process requires the 'researcher' to directly provide information mandatory for consent to the person (s), in this case the parents, which was not done.

  Schedule Y of the Drugs and Cosmetics Act states that, "*Paediatric Subjects are legally unable to provide written informed consent, and are dependent on their parent(s)/ legal guardian to assume responsibility for their participation in clinical studies. Written informed consent should be obtained from the parent/ legal guardian. However, all paediatric participants should be informed to the fullest extent possible about the study in a language and in terms that they are able to understand. Where appropriate, paediatric participants should additionally assent to enroll in the study. Mature minors and adolescents should personally sign and date a separately designed written assent form.*"

  Also, according to the ICMR guidelines[24], '*Before undertaking any trial, the investigator must ensure that… a parent or legal guardian of each child has given proxy consent; the assent of the child should be obtained to the extent of the child's capabilities such as in the case of mature minors from the age of seven years upto the age of 18 years.*

  However, we did not come across such a process for taking assent having taken place. The children being mature minors, both the above norms have been flouted.

  Contents of the consent form

- The form states that "If you are not willing to participate you will not lose any benefits that you are entitled to; you will not be fined". The mention of a fine in a form seeking consent seems unreasonable.

- The consent form states, "During administration of the vaccine to your daughter, if there are any severe side effects, we have trained health workers available with medicines". However, in reality, no follow-up treatment has been provided for girls who have been facing side effects, and these girls have had to be treated subsequently by their parents in private medical facilities.

- The ICMR guidelines clearly state that *all prospective participants must be given all the necessary information (including the nature and purpose of the study (stating it is research), duration of participation with number of participants, the procedures to be followed, investigations if any to be performed, no loss of benefits to the participant, the policy on compensation, availability of medical treatment for injuries or risk management and alternative treatments (if available), irrespective of their social and economic condition or status, or literacy or educational levels. They*

[24] ICMR (2006), *Ethical Guidelines for Biomedical Research on Human Subjects*, Selection of Special Groups as Research Participants, Pg 28.

must also be kept fully apprised of all the dangers arising in and out of the research so that they can appreciate all the physical and psychological risks as well as moral implications of the research whether to themselves or others. [25]

The Schedule Y of Drugs and Cosmetics Act has also provided a detailed 'checklist of essential elements to be included in the study subject's informed consent document' which includes – 'description of the procedures to be followed, reasonably foreseeable risks/discomforts to the subject, benefits to the subject, specific appropriate alternative procedures or therapies available to the subject'. The checklist is attached as an appendix to this report.

However, the consent form for this project does not include any information on compensation, procedures to be followed, alternative treatments if available or risk management as mandated by the ICMR guidelines, necessary for informed consent.

c. General information on cervical cancer and HPV vaccine

- Throughout the project period, the girls as well as the parents were (mis) informed that the vaccination would prevent uterine cancer or cervical cancer. The HPV immunization card states that the "HPV vaccine prevents HPV infection". However, the vaccine is effective on only 2 types of HPV[26] and that the vaccination is not a substitute for cervical cancer screening. All women, including those who are vaccinated should continue to have regular pap test screening. Even the official Gardasil website clearly mentions, *"GARDASIL may not fully protect everyone, and does not prevent all types of cervical cancer, so it's important to continue routine cervical cancer screenings. GARDASIL does not treat cervical cancer or genital warts".*[27] Why are poor girls and their families being blatantly misled?

- Information was provided verbally to the girls and their parents/wardens that the vaccine will provide life-long protection, has no side-effects and will not affect future fertility of the young girls. There is lack of conclusive data regarding the length of immunologic protection the vaccine confers against HPV subtypes 16 and 18.[28] Since the long term efficacy and protection by the vaccine is unknown, it cannot be claimed that even 60-70% protection will be achieved. Moreover, since the highest incidence of cancer of the cervix in India is in women above 35 years of age, a 3-dose schedule at the age of 10-14 years will clearly not be adequate without booster doses. However, there is not enough scientific evidence in hand to know the frequency, timing, dosage strength, safety and overall cost burden of the booster doses.

- The parents / wardens were given to understand that it was a very expensive vaccine that was being offered free of cost for a limited period of time, and that it would be a great loss for the girls if they did not avail of this opportunity.

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[25] ICMR (2006), *Ethical Guidelines for Biomedical Research on Human Subjects*, Informed Consent Process, Pg 21.
[26] The current HPV vaccine prevents infections, resulting from just two of the HPV subtypes (16 and 18) that may cause cervical cancer, and also HPV subtypes 6 and 11 that can lead to genital warts. The subtypes 16 and 18 account for 70% of the cases of invasive cervical cancer globally. But there are over 100 HPV subtypes.
[27] http://www.gardasil.com/ Accessed on September 11, 2009.
[28] Lippman A, Melynk R et. Al (2007),"Human papillomavirus, vaccines and women's health: questions and cautions" Canadian Medical Association Journal (CMAJ) 177.

4. The Sorry State of the State

- The HPV immunization cards as well as the banners have NRHM and PATH logos, while the consent form has the contact addresses of the District Immunization Officer and a PATH official. It is a matter of serious concern that a national public health programme has endorsed this project under NRHM, whose machinery in the State is actively involved in operationalizing this 'project'.

- While none of the public health set-ups in the *mandal* have pap smear facilities, the absence of a gynaecologist in the entire *mandal* of Bhadrachalam is appalling. Apart from the lack of public health infrastructure, the inadequate access to quality health care is apparent in this area, which is frequently prone to malaria, dengue, diarrhoea and other health problems.

- Given the state of the public health system, no government can afford this expensive vaccination that costs Rs. 9,000 for every woman in a country where we cannot give DPT (costing Rs. 3) to 50% of children of the country.[29]

- Regarding the reported deaths of four girls in the area, while the local authorities have refused to take cognizance of the probable association of their deaths with the vaccine, two of the deaths have been written off as suicides when the parents clearly state that they were not.

5. Public Private Partnerships

- The implementation of the 'demonstration project' by the Ministry of Health and Family Welfare (MOHFW), ICMR, PATH International and the State Government of Andhra Pradesh is a clear case of a Public Private Partnership (PPP), and highlights concerns around such PPPs, which are being implemented without any plan for overall health system reorganization, or any mechanisms to enforce transparency and accountability.

- There is a serious lack of clarity with regard to the role and accountability of international NGOs such as PATH and international funding agencies such as the Bill and Melinda Gates Foundation[30], when in fact, according to the ICMR guidelines, the principles of totality of responsibility clearly state that "…all *those directly or indirectly connected with the research or experiment including the researchers, those responsible for funding or contributing to the funding of the research, the institution or institutions where the research is conducted and the various persons, groups or undertakings who sponsor, use or derive benefit from the research, market the product (if any) or prescribe its use so that, inter alia, the effect of the research or experiment is duly monitored and constantly subject to review and remedial action at all stages of the research and experiment and its future use*".[31]

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[29] Memorandum submitted to the Union Minister, MOHFW on 1st October 2009 by health networks, women's groups and concerned individuals.
[30] http://www.hindu.com/2010/04/08/stories/2010040857390100.htm
[31] Indian Council of Medical Research, 2006, Ethical Guidelines for Biomedical Research on Human Subjects, Pg 7

- Moreover, it is evident that unless the cost of this vaccine becomes a fraction (around 5%) of what it is today, there is no possibility that it can be incorporated into the National Immunization Programme. Since this is an unsustainable public private partnership, the state should reflect on the rationality of this project. Even if the vaccine is proved to be safe, it will be highly unaffordable.

6. Adverse Events under reported

- Amongst side effects reported by girls in Bhadrachalam, there have been many instances of mood swings, irritability and agitation, seizures and a general feeling of uneasiness. Other reported side effects have included severe headaches and stomach-aches, dizziness, early onset of menstruation soon after the vaccination and heavy bleeding in some cases.
  The official Gardasil website clearly mentions, *"The side effects listed include, pain, swelling, itching, bruising and redness at the injection site, headache, fever, nausea, dizziness, vomiting, and fainting. Sometimes fainting is accompanied by falling with injury, as well as shaking or stiffening and other seizure-like activity"*.[32]

  Most of these side effects were not mentioned in the consent form.

  The ICMR guidelines assert that *every research must include an in-built mechanism for compensation for the human participants, either through insurance or any other appropriate means, to cover all foreseeable and unforeseeable risks, by providing for remedial action and comprehensive aftercare, including treatment during and after the research or experiment, in respect of any effect that the conduct of research or experimentation may have on the human participant and to ensure that immediate recompense and rehabilitative measures are taken in respect of all affected, if and when necessary*.[33]

  Given that this 'study' is being conducted in collaboration with the ICMR, it is all the more inexcusable, that the Council has not taken any measures to ensure that the code of ethics is not violated.

[32] http://www.gardasil.com/ Accessed on September 11, 2009.
[33] Indian Council of Medical Research, 2006, Ethical Guidelines for Biomedical Research on Human Subjects, – *Informed Consent Process*

OUR RECOMMENDATIONS AND DEMANDS

- All trials using HPV vaccines should be stopped pending an impartial inquiry by the Government that looks into:
    - the reported deaths of the tribal girls;
    - the side effects of the vaccine on affected girls, so that responsibility can be fixed and action taken.

- All the children going through side effects should be provided proper and free medical treatment and follow up.

- The state government should take immediate action, which includes providing compensation to the families who have lost their children and to the children suffering side-effects. The government should make sure that all these projects are immediately brought to a halt across the country, until concerns relating to safety, efficacy and cost effectiveness of the planned interventions have been re-evaluated.

- No organization/ establishment should be given permission for clinical trials/demonstration projects/ vaccine administration, without systematic approval, a sound and ethical methodology of conducting the study and without provision of constant monitoring by the state, regardless of the vaccine being administered. Financial support from the industry or from an international organization should not be the criterion to introduce a vaccine, whether in a pilot project or in the national immunization programme.

- The government should place before the public:
    - All documents related to this vaccine on the basis of which the Drug Controller has given permission.
    - All the documents pertaining to the agreement with vaccine manufacturers and all other bodies regarding the government's plan to introduce the HPV vaccine.
    - The list of vaccination / HPV projects planned, proposed, approved and completed, the agencies involved, the donors involved, proposed locations and all the results of the clinical trials / demonstration projects.
    - The estimated total cost, as per the government's assessment, of purchase of the vaccine and its administration.

- The state should focus on providing population-based outreach pap screening services for cancer of cervix, particularly for women from the tribal and rural areas.

- Special measures should be undertaken for the promotion of awareness among women in particular and the community in general, so that women can come forward without any inhibitions to undergo such screening tests.

- Instead of an expensive vaccination strategy, monitoring measures should be made available to detect cervical cancer at a very early stage.

- There should be a national pro-people vaccine policy based on public health needs.

Acknowledgements

We, Sarojini, Anjali and Ashalata, would like to acknowledge all those who made this visit possible and were part of this critical process to document the ground realities vis-à-vis the 'demonstration project'. We are very thankful to N. Madhusudhan and Dr Sagari Ramdas for making the visit possible by providing us the contacts and facilitating different aspects of the visit. We specially thank K Srinivas and M Ramanamma for their support during this visit. We would also like to thank Sudha Sundararaman and P. Jyoti for putting us in touch with their members in the area.

Most of all, we are grateful to the children and parents who came forward to talk to us. Thanks are due to parents of K Sarita, who despite the loss of their daughter have been a symbol of courage and commitment. We specially thank M Renuka, other members of AIDWA and other *adivasi sanghatans* for arranging meetings and providing us contacts and information. We would like to acknowledge the wardens, teachers, assistants and health staff who provided us with the details.

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APPENDIX

DRUGS AND COSMETICS (IIND AMENDMENT) RULES, 2005 (EXCERPT)

A checklist of essential elements to be included in the study subject's informed consent document as well as a format for the informed Consent Form for study Subjects is given in Appendix V.

Appendix V

INFORMED CONSENT

1. Checklist for study Subject's informed consent documents

1.1. Essential Elements:

1. Statement that the study involves research and explanation of the purpose of the research
2. Expected duration of the Subject's participation
3. Description of the procedures to be followed, including all invasive procedure and
4. Description of any reasonably foreseeable risks or discomforts to the Subject
5. Description of any benefits to the Subject or others reasonably expected from research. If no benefit is expected Subject should be made aware of this.
6. Disclosure of specific appropriate alternative procedures or therapies available to the Subject.
7. Statement describing the extent to which confidentiality of records identifying the Subject will be maintained and who will have access to Subject's medical records
8. Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomized trials)
9. Compensation and/or treatment(s) available to the Subject in the event of a trial-related injury
10. An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury
11. The anticipated prorated payment, if any, to the Subject for participating in the trial
12. Subject's responsibilities on participation in the trial
13. Statement that participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which the Subject is otherwise entitled
14. Any other pertinent information

1.2 Additional elements, which may be required

a. Statement of foreseeable circumstances under which the Subject's participation may be terminated by the investigator without the Subject's consent.

b. Additional costs to the Subject that may result from participation in the study.

c. The consequences of a Subject's decision to withdraw from the research and procedures for orderly termination of participation by Subject.

d. Statement that the Subject or Subject's representative will be notified in a timely manner if significant new findings develop during the course of the research which may affect the Subject's willingness to continue participation will be provided.

e. A statement that the particular treatment or procedure may involve risks to the Subject (or to the embryo or fetus, if the Subject is or may become pregnant), which are currently unforeseeable

f. Approximate number of Subjects enrolled in the study

2. Format of informed consent form for Subjects participating in a clinical trial

Infomed Consent form to participate in a clinical trial

Study Title:

Study Number:

Subject' Initials:_____ Subject's Name:_____

Date of Birth / Age:_____

Please initial box (Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date:_____/_____/_____

Signatory's Name: _____

Signature of the Investigator:_____ Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness _____

Date_____/_____/_____

Name of the Witness: _____

GOVERNMENT OF INDIA
MINISTRY OF HEALTH AND FAMILY WELFARE
DEPARTMENT OF HEALTH RESEARCH

ANNEXURE P/13

LOK SABHA
UNSTARRED QUESTION NO. 800
TO BE ANSWERED ON 07 TH FEBRUARY, 2025

HPV VACCINATION

800. MR. PRADYUT BORDOLOI:

Will the Minister of **HEALTH AND FAMILY WELFARE** be pleased to state:

(a) The details of the incidence of Human Papillomavirus (HPV) in India and the North Eastern region (NER) during the last five years :

(b) The details of the recommendations of the National Technical Advisory Group for Immunization with regards to the HPV vaccine:

(c) Whether the government plans to include the HPV vaccine within the National Immunization program; and

(d) If so, the details thereof along with the timeline of the implementation for the same and if not the reasons therefore?

ANSWER
THE MINISTER OF STATE IN THE MINISTRY OF HEALTH AND FAMILY WELFARE
(SHRI PRATAP RAO JADHAV)

(a) : Presently, no such consolidated data on countrywide incidence of Human Papillomavirus (HPV) is available. However, Indian Council of Medical Research (ICMR) has informed that 83.2 per cent of invasive cervical cancers are attributed to HPVs 16 or 18. As per the National Cancer Registry Program (ICMR-NCRP) report, 2020, State/UT wise list of the estimated number of incidence of cervical cancer cases from 2019-2023 is enclosed in Annexure- I.

(b) : National Technical Advisory Group on immunization (NTAGI) has informed that the 17th NTAGI meeting, held on 28th June 2022, recommended the introduction of the HPV vaccine in the Universal Immunization Program (UIP).

(c) and (d) : The Universal Immunization Program (UIP) provides 11 vaccines against 12 Vaccine Preventable Diseases (VPDs). However the HPV vaccine is not a part of the Universal Immunization Program (UIP).

Annexure I

Estimated Incidence of cancer cases in India by different State/UT - Cervical cancer (ICD10: C53) - (2019-2023)					
State	**2019**	**2020**	**2021**	**2022**	**2023**
Jammu & Kashmir	612	632	648	666	684
Ladakh	15	16	16	16	17
Himachal Pradesh	461	474	483	495	506
Punjab	2223	2280	2339	2399	2459
Chandigarh	58	58	60	62	63
Uttaranchal	594	608	624	639	656
Haryana	1486	1536	1580	1630	1678
Delhi	1217	1259	1303	1348	1394
Rajasthan	3620	3721	3822	3927	4034
Uttar Pradesh	9793	10046	10301	10559	10825
Bihar	4941	5073	5207	5348	5489
Sikkim	26	26	27	29	29
Arunachal Pradesh	68	71	74	75	78
Nagaland	114	116	121	124	127
Gujarat	101	103	107	112	117
Mizoram	134	139	143	147	153
Tripura	185	191	194	199	204
Meghalaya	109	111	113	117	123
Assam	1754	1802	1851	1900	1952
West Bengal	5534	5679	5823	5971	6119
Jharkhand	1723	1770	1821	1874	1926
Odisha	2595	2656	2717	2778	2844
Chhattisgarh	1467	1507	1545	1584	1626
Madhya Pradesh	3934	4042	4151	4264	4378
Gujarat	3637	3738	3840	3943	4048
Daman	9	9	9	10	12
Dadra & Nagar Haveli	15	15	15	16	17
Maharashtra	6545	6708	6872	7037	7207
Telangana	2466	2532	2595	2665	2731
Andhra Pradesh	3713	3799	3886	3973	4063
Karnataka	4419	4536	4657	4776	4900
Goa	101	104	106	107	109
Lakshadweep	4	4	4	4	6
Kerala	1699	1734	1771	1804	1840
Tamil Nadu	7768	7958	8144	8337	8534
Pondicherry	128	133	138	143	148
Andaman & Nicobar Islands	21	23	23	25	25
Total	**73289**	**75209**	**77130**	**79103**	**81121**

Reference: National Cancer Registry Program report, 2020

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ANNEXURE P/14

India

SII to manufacture India's first qHPV vaccine against cervical cancer after DCGI approval

PAYAL BANERJEE 12 July, 2022 05:01 pm IST



Inside a vaccine lab at Serum Institute of India | Representational image | Twitter

New Delhi: The Drugs Controller General of India (DCGI) on Tuesday granted market authorisation to Serum Institute of India (SII) to manufacture indigenously-developed India's first Quadrivalent Human Papillomavirus vaccine (qHPV) against cervical cancer, official sources said.

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DCGI's approval comes following recommendation by the Subject Expert Committee (SEC) on COVID-19 of the CDSCO on June 15 over the same Prakash Kumar Singh, director (government and regulatory affairs) at Serum Institute, had applied to the DCGI seeking market authorisation of qHPV after the phase 2/3 clinical trial was completed with support of the Department of Biotechnology to ensure its early availability, official sources said.

The government advisory panel NTAGI had recently also approved the qHPV after reviewing the clinical trial data of the vaccine.

In the application to the DCGI, Singh is learnt to have stated that qHPV vaccine CERVAVAC has demonstrated robust antibody response that is nearly 1,000 times higher than the baseline against all targeted HPV types and in all dose and age groups.

In the application, Singh had mentioned that lakhs of women are diagnosed every year with cervical cancer as well as few other cancers and death ratio is also very high.

Cervical cancer in India ranks as the second most frequent cancer among women between 15 and 44 years of age.

"Also, it is noteworthy that presently our country is fully dependent on foreign manufacturers for the HPV vaccine. In line with the phi[illegible] of our group & under leadership of our CEO, Dr Adar C Poonawalla, it has alw[illegible] available high quality 'Made in India' vaccines at afford[illegible] and world at large," Singh mentioned in the application.

[illegible] conditioning? Here's what you'll do by 2050...
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ANNEXURE P/15

India to launch HPV vax drive for 14-year-old girls this month

TNN | Feb 25, 2026, 05.54 AM IST



India to launch HPV vax drive for 14-year-old girls this month

NEW DELHI: In a major preventive health push against cervical cancer, the Centre is set to roll out a nationwide human papillomavirus (HPV) vaccination drive for 14-year-old girls later this month, offering the shot free of cost at govt health facilities across the country.

The campaign will target girls turning 14 each year, covering an annual cohort of approximately 1.2 crore adolescents across India. The vaccination will be voluntary and provided at designated govt health centres.

Cervical cancer is the second most common cancer among Indian women, which causes nearly 80,000 new cases and over 42,000 deaths annually. Persistent infection with high-risk HPV types, particularly 16 and 18, accounts for more than 80% of cases.

The move follows sustained emphasis at the highest level. PM Modi has repeatedly highlighted cervical cancer prevention, calling for vaccination, early screening and affordable treatment, including at the Quad Cancer Moonshot event in Sept 2024.

Unlike routine immunisation under the Universal Immunisation Programme, the HPV drive will be conducted as a special campaign on designated immunisation days and tracked through the U-WIN digital platform to ensure rapid coverage.

The vaccine, Gardasil, protects against HPV types 16 and 18, along with 6 and 11. Gavi has committed 2.6 crore

doses, with about 1.5 crore already delivered. Officials estimate roughly almost 1.2 crore doses will be needed annually to cover girls turning 14 each year.

Globally, over 500 million doses of the vaccine have been administered.

Dr Abhishek Shankar from the department of radiation oncology at AIIMS described the rollout as a historic step that strengthens India's push to eliminate cervical cancer, protect lakhs of girls from a preventable disease and reduces the future treatment burden in line with the WHO elimination goal.

Dr Pragya Shukla, head of clinical oncology at Delhi State Cancer Institute, said, "vaccination before sexual debut is critical, as HPV infection is silent and irreversible, and the vaccine is safe and proven".

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CLAIMS JOURNAL

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Merck to Settle Bulk of Gardasil Suits for About $50 Million

Merck & Co. says it will settle a spate of lawsuits that blame the drugmaker's blockbuster Gardasil cancer vaccine for causing autoimmune ailments that affect young women's hearts and reproductive systems for an amount that is "not material" to the pharma firm.

Gardasil prevents human papillomavirus, or HPV infections. Under the accord, Merck would pay more than $50 million to settle more than 200 cases, according to people familiar with the matter. The deal would also resolve a closely watched case set for trial next month in state court in Los Angeles.

Merck, based in Rahway, New Jersey, said in an emailed statement to Bloomberg News that it decided to "end the litigation in its entirety" by settling all the Gardasil litigation — except for one case. The company added that research and evidence "continues to support the safety and efficacy of our HPV vaccines." Researchers have tied HPV infections to cervical cancer.

In mass-injury litigation like the Gardasil cases, companies can agree to pay a group of people claiming a product hurt them to resolve cases without saying that the product was harmful. Merck isn't admitting liability as part of settlement, said the people, who asked not to be identified discussing details that remain private.

An attorney in the Los Angeles case involving Jennifer Robi, a California woman who contended Gardasil she got as a teenager caused a heart ailment that's left her in a wheelchair, declined to comment. Her case could have been the first against Merck over the vaccine to be decided by a jury.

The vaccine has been approved for use in about 150 countries since it was introduced 20 years ago and Merck says more than 900 million doses of its Gardasil and Gardasil 9 products have been distributed worldwide. Mainstream medicine has heralded it as safe and effective for decades. Merck has steadfastly denied the shot causes dangerous side effects.

In its annual report in February, the company said it had "entered into a proposed agreement" in October to end the litigation that required additional steps to finalize. Merck officials said the deal only would be consummated if enough people who had received Gardasil signed on.

Merck said in its statement on the settlement that the amount it would pay is "considerably less than Merck's anticipated costs" in defending the cases.

From its inception, Gardasil was consistently a big seller for Merck and recorded dramatic growth in the early 2020s. It hit $8.9 billion in 2023 sales before the introduction of low-cost rivals in China led to a decline over the last two years.

Health and Human Services Secretary Robert F. Kennedy Jr., a veteran plaintiffs' lawyer and vaccine skeptic, had helped prepare Robi's claims for trial before he was appointed the nation's top health official last year by President Donald Trump.

Kennedy, who had been in line to receive 10% referral fees on successful Gardasil lawsuits, has waived his right to collect that money, Bloomberg News has reported.

Merck avoided a showdown over Gardasil in North Carolina last year when a judge dismissed a group of more than 200 cases he concluded were preempted by the US Food and Drug Administration's approval of the vaccine's labeling. The judge also found "no scientist could reasonably conclude" the vaccine caused the alleged maladies "based on this paucity of evidence" offered by the plaintiffs' expert witnesses.

Those cases are part of the deal, said the people familiar with the matter.

It's a tricky time for vaccine manufacturers as they face unprecedented scrutiny under Kennedy, who has questioned vaccine safety for years.

In March, a judge temporarily blocked Kennedy's effort to scale back the list of recommended childhood vaccinations, including the suggestion that young people get one HPV shot instead of as many as three. Kennedy is appealing the ruling, as is Children's Health Defense, the non-profit he formerly led that has campaigned against immunizations.

The Los Angeles case is Robi v. Merck, BC628589, California Superior Court, County of Los Angeles.

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ANNEXURE P/17

2019 SCC OnLine Del 11929

In the High Court of Delhi at New Delhi

(BEFORE VIBHU BAKHRU, J.)

W.P. (C) 343/2019 & CM Nos. 1604-1605/2019

Master Haridaan Kumar and Others … Petitioners;

Versus

Union of India and Another … Respondents.

And

W.P. (C) 350/2019 & CM Nos. 1642-1644/2019

Baby Veda Kalaan and Others … Petitioners;

Versus

Directorate of Education and Others … Respondents.

W.P. (C) 343/2019, CM Nos. 1604-1605/2019, W.P. (C) 350/2019 and CM Nos. 1642-1644/2019

Decided on January 22, 2019

Advocates who appeared in this case:

Mr. Anubhav Kumar and Mr. Abhinav Mukherji, Advocates.

Mr. Ramesh Singh, Standing Counsel, GNCTD with Mr. Chirayu Jain and Ms. Nikita Goyal, Advocates for GNCTD.

Mr. Sushil Kumar Pandey, Senior Panel Counsel with Ms. Neha Sharma, Advocates for UOI with Dr. Pradeep Haldar (Deputy Commissioner (IMM) Incharge).

Ms. Diya Kapur, Ms. Shyel Trehan and Mr. Rishabh Sharma, Advocates.

Mr. Ramesh Singh, Standing Counsel, GNCTD with Mr. Santosh Kumar Tiwari, ASC, Mr. Chirayu Jain and Ms. Nikita Goyal, Advocates for GNCTD.

Ms. Monika Arora, CGSC for R-2/UOI with Mr. Harsh Ahuja and Mr. Praveen Singh, Advocate for UOI.

The Order of the Court was delivered by

VIBHU BAKHRU, J.:— The petitioners have filed the above-captioned petitions, *inter alia*, impugning the notification No. DE.23 (386)/Sch.Br./2018 dated 19.12.2018 (hereafter 'the impugned notification') issued by the Directorate of Education (DoE), Government of National Capital Territory of Delhi. By the impugned notification, the Directorate of Education (DoE) has directed the Chairman/Manager/Principal to direct all schools (whether Government, Government Aided and Private Unaided Recognised schools) to comply

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with certain guidelines relating to implementation of the Measles and Rubella (MR) vaccination campaign. Under the said campaign, MR vaccines are to be administered to all children aged between nine months and fifteen years (the beneficiaries). The said guidelines, *inter alia*, provide that no consent would be required from the beneficiaries/their parents for implementing the MR Campaign.

2. The petitioners are, essentially, aggrieved by the decision of the respondents to forcibly administer MR vaccination without the consent of the parents/guardians or family members of the beneficiaries (children aged between nine months to fifteen years). The petitioners in W.P. (C) 350/2019 pray that the impugned notification be set aside and further directions be issued that no vaccination be administered in cases where there is parental objection to such vaccination. The petitioners in W.P. (C) 343/2019, *inter alia*, pray that an order be issued to the respondents restraining them from forcibly administering vaccinations to children without the consent of their parents/guardians.

3. On 15.01.2019, this Court had observed that the contention of the petitioners, that children cannot be administered vaccination forcibly and without the parental consent, is merited. Mr. Singh, learned counsel appearing for DoE and Government of NCT of Delhi (respondent nos. 1 and 2) did not dispute the said proposition that readily accepted that vaccination cannot be administered forcibly and without the consent of the parents.

4. He, however, submitted that an express affirmative consent from parents/guardians of the beneficiaries ought not to be a pre-condition for administering the said vaccine. He contended that such consent of the parents/guardians should be inferred unless they expressly state in the negative. He referred to the same as "*opt-out consent*".

5. Plainly, in order for any parent or guardian to give his/her consent (whether expressly or by inference), it would be necessary for such parent or guardian to have complete information with regard to the proposed vaccination campaign. Clearly, for any parent or guardian to take an informed decision, it would be necessary for such parent to be aware of (a) the vaccine proposed to be administered; (b) contraindications or side effects of such vaccine; (c) the date on which such vaccine administered to the ward/children; and (d) the personnel who would administer the same.

6. Mr. Raj Shekhar Rao and Ms. Diya Kapur, learned counsel advanced arguments on behalf of the petitioners and Mr. Ramesh Singh advanced arguments on behalf of respondent nos. 1 and 2. It was apparent from the said arguments that learned counsel for both the sides were *ad idem* that vaccination could not be administered to children without consent of their parents/guardians. Mr. Pandey, learned counsel appearing for the Union of India, did not advance any

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submissions apart from stating that the MR Campaign was successfully implemented in twenty-six states of the country.

7. In view of the above, impugned notification, to the extent it provides that no consent is required for the beneficiaries and/or their parents, is quashed.

8. Mr. Singh, also readily agreed, on instructions, that information with regard to MR. campaign would require to be disseminated. He also handed over a tabular statement indicating the names of daily newspapers in English, Hindi, Urdu and Punjabi, which would carry the advertisements. It was also submitted that advertisements would be of a quarter page and would indicate the material information. It was also agreed that the said information would be put up on the website of DoE.

9. In view of the above, the controversy between the parties was narrowed down, essentially, on two issues, (a) whether an express consent of the parents/guardians was necessary or whether the same could be inferred by silence on the part of the concerned parents/guardians; and (b) whether the respondents were required to indicate the contraindications and the side effects of the vaccines in the newspaper advertisements as well as in other literature to be provided to parents/guardians of the beneficiaries.

10. Insofar as the first issue is concerned - that is, whether an express consent from parents/guardians is necessary - Mr. Singh contended that the vaccination campaign is required to cover at least 95% of the beneficiaries within a short span of time for the same to be successful and, therefore, there would not be enough time for respondents to elicit a positive express response from the parents/guardians. He had further submitted that there are a large number of students from EWS categories and it would be very difficult to ensure a response from the parents of such students. He further submitted that the respondents would also have no opportunity to counsel such parents.

11. Ms. Diya Kapur countered the aforesaid submissions. She submitted that she had contacted certain schools and the data indicated that parents of EWS students, in most cases, had responded to the consent forms sent by the concerned schools. She referred to the case of one such school (Bal Bharti), where consent forms were sent to 856 students from the EWS category and 812 such consent forms were received back. Out of the aforesaid, 394 had not agreed for administration of the MR vaccine. She further contended that the contention of the respondents, that it is difficult to contact students from EWS category, is without basis. She further referred to various newspaper reports, which had reported incidents where the children had fallen sick after administration of the MR vaccine. She contended

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that it was, thus, necessary for parents to take an informed decision.

12. Mr. Singh, countered the aforesaid submissions and submitted that vaccination was a necessary measure for eradication of the diseases in question and those children, who are not vaccinated, may act as a disease vector putting the general health of others at risk. He contended that in larger public interest, it was necessary that the MR campaign be supported by all measures.

13. Undisputedly, there is an urgent need to disseminate information regarding the MR campaign and the assumption that children could be vaccinated forcibly or without consent is unsustainable. This Court is of the view that all efforts are required to be made to obtain the decision of the parents before proceeding with the MR campaign. In this regard, it would be apposite to ensure that the consent forms/slips are sent to each and every student. Since the time period for implementing the campaign is short, the response period should be reduced and parents/guardians of students must be requested to respond immediately and, in any case, in not more than three working days. If the consent forms/slips are not returned by the concerned parent, the class teacher must ensure that the said parents are contacted telephonically and the decision of such parent is taken on phone. The concerned teacher ought to keep full records of such decisions received telephonically. In respect of those parents/guardians that neither return the consent slips nor are available telephonically despite efforts by the concerned teacher, their consent can be presumed provided respondent nos. 1 and 2 ensure that full information regarding the commission is provided to all parents.

14. The contention that indication of the side effects and contraindications in the advertisement would discourage parents or guardians from consenting to the MR campaign and, therefore, the same should be avoided, is unmerited. The entire object of issuing advertisements is to ensure that necessary information is available to all parents/guardians in order that they can take an informed decision. The respondents are not only required to indicate the benefits of the MR vaccine but also indicate the side effects or contraindications so that the parents/guardians can take an informed decision whether the vaccine is to be administered to their wards/children.

15. In view of the above, it is directed as under:

(1) Directorate of Family Welfare shall issue quarter page advisements in various newspapers as indicated by the respondents, namely, The Hindustan Times, The Times of India, The Hindu, The Pioneer, The Indian Express, Delhi Tribune, Mail Today, The Asian Age, Navbharat Times, Dainik Jagran, Punjab Kesari, Hindustan, Amar Ujala, Navodaya Times, Hamara Samaj, Pratap, Daur-e-Jadeed, Jathedar, Jan Ekta. The advertisements

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shall also indicate that the vaccination shall be administered with Auto Disable Syringes to the eligible children by Auxiliary Nurse Midwifery. The advertisement shall also clearly indicate the side effects and contraindications as may be finalised by the Department of Preventive Medicine, All India Institute of Medical Sciences.

(2) The Head of Department of Preventive Medicine, All India Institute of Medical Sciences is directed to finalise the list of contraindications and risks associated with the vaccine being included in the aforesaid advertisements. Advertisements in two of the newspapers (one in English and the other in Hindi language) will also indicate the dates on which MR vaccine will be administered in respective schools. The website of DoE shall also clearly set out the above information.

(3) The School shall issue consent forms to parents of all students admitted in their schools up to Class X with instructions that the forms be returned to the school within a period of two working days. The class teacher/nodal teacher shall contact parents/guardians of students who have not returned the consent forms within a period of one working day thereafter and elicit their consent or objection to administration of such vaccines. The class teacher/nodal teacher shall keep a record of the decision of the parents so contacted. In the event the class teacher/nodal teacher is unable to reach parents despite best efforts, the record of the efforts made shall be duly noted by her.

(4) MR vaccines will not be administered to those students whose parents/guardians have declined to give their consent. The said vaccination will be administered only to those students whose parents have given their consent either by returning the consent forms or by conforming the same directly to the class teacher/nodal teacher and also to students whose parents/guardians cannot be contacted despite best efforts by the class teacher/nodal teacher and who have otherwise not indicated to the contrary.

16. It will be open for the DoE/Department of Health to approach the parents directly to inform them and educate them regarding the MR vaccine campaign in order to elicit their consent.

17. Mr. Singh had submitted that under the present MR Vaccination campaign, DoE is targeting 55 lakh children in the age group of nine months to fifteen years. of these 55 lakh children, approximately 34 lakh children are attending recognised schools; approximately 10-11 lakh children are attending unrecognised private/pre-nursery schools; and the remaining 10-11 lakh children are either not attending any

school or are below the age of 3 years and are living with their parents/guardians.

18. It is made clear that the directions set out above relate only to students attending recognized schools. In respect of the remaining children, the respondents seek time of two to three weeks to submit the modalities of obtaining consent. Once these have been submitted, the court shall consider the conditions on which the MR campaign in respect of the remaining unrecognised private/pre-nursery schools and children not attending school shall proceed.

19. List for further proceedings on 01.02.2019.

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ANNEXURE P/18

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Health and Economic Implications of HPV Vaccination in the United States

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From the Department of Health Policy and Management, Harvard School of Public Health, Boston

Abstract

BACKGROUND—The cost-effectiveness of prophylactic vaccination against human papillomavirus types 16 (HPV-16) and 18 (HPV-18) is an important consideration for guidelines for immunization in the United States.

METHODS—We synthesized epidemiologic and demographic data using models of HPV-16 and HPV-18 transmission and cervical carcinogenesis to compare the health and economic outcomes of vaccinating preadolescent girls (at 12 years of age) and vaccinating older girls and women in catch-up programs (to 18, 21, or 26 years of age). We examined the health benefits of averting other HPV-16–related and HPV-18–related cancers, the prevention of HPV-6–related and HPV-11–related genital warts and juvenile-onset recurrent respiratory papillomatosis by means of the quadrivalent vaccine, the duration of immunity, and future screening practices.

RESULTS—On the assumption that the vaccine provided lifelong immunity, the cost-effectiveness ratio of vaccination of 12-year-old girls was $43,600 per quality-adjusted life-year (QALY) gained, as compared with the current screening practice. Under baseline assumptions, the cost-effectiveness ratio for extending a temporary catch-up program for girls to 18 years of age was $97,300 per QALY; the cost of extending vaccination of girls and women to the age of 21 years was $120,400 per QALY, and the cost for extension to the age of 26 years was $152,700 per QALY. The results were sensitive to the duration of vaccine-induced immunity; if immunity waned after 10 years, the cost of vaccination of preadolescent girls exceeded $140,000 per QALY, and catch-up strategies were less cost-effective than screening alone. The cost-effectiveness ratios for vaccination strategies were more favorable if the benefits of averting other health conditions were included or if screening was delayed and performed at less frequent intervals and with more sensitive tests; they were less favorable if vaccinated girls were preferentially screened more frequently in adulthood.

CONCLUSIONS—The cost-effectiveness of HPV vaccination will depend on the duration of vaccine immunity and will be optimized by achieving high coverage in preadolescent girls, targeting initial catch-up efforts to women up to 18 or 21 years of age, and revising screening policies.

In the united states, cervical cancer developed in an estimated 11,150 women and caused death in 3600 women in 2007.1 Infection with high-risk “oncogenic” types of human papillomavirus (HPV) is the cause of 100% of cervical cancers, 90% of anal cancers, 40% of vulvar and vaginal cancers, at least 12% of oropharyngeal cancers, and 3% of oral cancers.2 Worldwide, HPV types 16 (HPV-16) and 18 (HPV-18) cause approximately 70% of cases of cervical cancer.3›4

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No potential conflict of interest relevant to this article was reported.

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Vaccines against HPV-16 and HPV-18 appear to be highly efficacious in preventing HPV-16 and HPV-18 infections and cervical lesions in girls and women who have not previously been infected with these types.[5–9] The vaccine currently licensed in the United States also prevents HPV types 6 and 11 (HPV-6 and HPV-11), which are responsible for most genital warts and juvenile-onset recurrent respiratory papillomatosis.[10]

There are important questions regarding the appropriate target population for prophylactic vaccination against HPV-16 and HPV-18. Since the vaccine is most efficacious before the onset of sexual activity, most investigators agree that the target population for routine immunization should be adolescents who are approximately 12 years of age.[11,12] Recommended temporary catch-up programs to provide vaccine coverage to girls and women 13 years of age and older range from an upper age limit of 18 to 26 years.[11,12]

The impact of HPV vaccination on the rate of cervical cancer will not be observable for decades; thus, decisions regarding a vaccination policy will inevitably rely on studies reporting intermediate outcomes. Estimating the magnitude of the benefit of vaccination is further complicated when one considers the extensive secondary-prevention program in the United States. This program, which involves the use of cytology-based screening, is recommended annually or biennially, starting 3 years after the first sexual intercourse and no later than 21 years of age.[13–15] HPV DNA testing is recommended as a triage test for equivocal results of cytologic analysis and in combination with cytologic tests for primary screening in women 30 years of age or older.[16]

Before long-term data become available, mathematical models used in a decision-analytic framework that synthesize the best available data while ensuring consistency with epidemiologic observations can project outcomes beyond those reported in clinical trials, provide insight into key drivers of cost-effectiveness, and be revised as new information emerges. Extending previous studies of HPV vaccination,[17–22] we evaluated the cost-effectiveness of vaccinating 12-year-old girls and of temporary catch-up programs. We considered the dynamics of HPV transmission, the duration of vaccine efficacy, the potential benefits of preventing noncervical HPV-related conditions, the anticipated changes in screening practice, and potential disparities in access to care.

METHODS

ANALYTIC OVERVIEW

Synthesizing epidemiologic, clinical, and demographic data from the United States, we used empirically calibrated simulation models to estimate the lifetime costs and benefits of vaccinating 12-year-old girls (herein referred to as the vaccination of preadolescent girls), as well as catch-up programs in girls and women up to 18, 21, or 26 years of age, in the context of current cytology-based screening in the United States. The base-case analysis was intended to be relevant to both the bivalent and quadrivalent HPV vaccines and therefore focused on the outcomes of cervical cancer. To examine the additional benefits of the vaccine for which empirical data were available, we also assessed the effect of the quadrivalent vaccine on HPV-6–associated and HPV-11–associated genital warts. Although the efficacy of the vaccine against noncervical HPV-16–associated and HPV-18–associated cancers and HPV-6–associated and HPV-11–associated juvenile-onset recurrent respiratory papillomatosis is more uncertain, we assessed the effect of their inclusion on our results. Although we assumed lifelong complete protection against the vaccine-targeted types of HPV in the base-case analysis, we evaluated the effect of waning vaccine-induced immunity (without and with a booster). Other uncertainties that we evaluated included cross-protection of the vaccine against high-risk types of HPV that did not include HPV-16 and HPV-18, the

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increased incidence of high-risk types of HPV that did not include HPV-16 and HPV-18, disparities in vaccination and screening coverage, and revisions in screening practices.

We adopted a societal perspective, discounted costs and benefits by 3% annually, and expressed benefits as quality-adjusted life-years (QALYs) gained. After eliminating strategies that were more costly and less effective or less costly and less cost-effective than an alternative strategy, incremental cost-effectiveness ratios were calculated as the additional cost divided by the additional health benefit associated with one strategy as compared with the next-less-costly strategy. Although there is no consensus on a cutoff point for good value for resources, we interpreted our results in terms of a commonly cited threshold of $50,000 per QALY gained, as well as an upper-bound threshold of $100,000 per QALY gained.23

MODELS

We used a flexible modeling approach that included a dynamic model to simulate the sexual transmission of HPV-16 and HPV-18 infections between men and women and an individual-based stochastic model to simulate the cervical carcinogenesis associated with all types of HPV. Both models have been described previously.24›25 Briefly, the dynamic model is an open-cohort, age-structured compartmental model in which women and men form sexual partnerships over time. Women and men enter the susceptible pool on sexual initiation starting at 10 years of age, and with each partnership, HPV-16 or HPV-18 may be transmitted, depending on the number of new partners, the prevalence of HPV among the opposite sex, and the probabilities of transmission of HPV-16 and HPV-18 from an infected partner. After the first HPV infection and clearance, partial type-specific natural immunity develops, effectively reducing a person's susceptibility to future infections of the same type. Grade 1 cervical intraepithelial neoplasia (CIN 1) or grade 2 or 3 CIN (CIN 2/3) can develop in women with HPV-16 or HPV-18 infection, and invasive cancer may develop in women with CIN 2/3.

The individual-based stochastic model has a similar structure. However, all types of HPV (categorized as HPV-16, HPV-18, other high-risk types of HPV, and low-risk types of HPV) are included, the incidence of HPV is a function of age and individual-level characteristics, it keeps track of each person's history (e.g., vaccination, screening, treatment, and past abnormalities), and it can accommodate complex screening strategies.25›26 The dynamic model was used to estimate reductions in the age-specific incidence of HPV-16 and HPV-18 with vaccination, reflecting the direct benefits to persons who were vaccinated, as well as indirect benefits, because of herd immunity, to those who were not vaccinated. The generated reductions in the incidence of HPV-16 and HPV-18 served as inputs to the stochastic model, which was used to compare multiple strategies for the prevention of cervical cancer. The specific features of the individual-based stochastic model allowed us to identify the synergies between vaccination and screening, study the implications of disparities in vaccination and screening coverage, assess the effect of cross-protection to other types of HPV, and explore the potential for an increase in the incidence of types of HPV that were not targeted by the vaccine.

The initial variables from the models were based on data from epidemiologic studies, cancer registries, and demographic statistics. The models were calibrated with the use of a likelihood-based approach to fit to empirical data, such as the age-specific prevalence of HPV, the age-specific incidence of cervical cancer, and the distribution of types of HPV observed among girls and women in the U.S. population.3›4›27–31 These approaches have been described elsewhere,24›25 and details relevant to the current analysis are provided in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

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For noncervical cancer conditions, data included the incidence of other HPV-16–associated and HPV-18–associated cancers; the incidence of low-risk, HPV-associated genital warts and juvenile-onset recurrent respiratory papillomatosis; the proportion of each disease attributable to vaccine-targeted types of HPV; and the disease-specific quality of life, costs, and mortality2,10,32–41 (Table 1). Costs (in 2006 U.S. dollars) included the direct medical costs associated with screening, diagnosis, and treatment (e.g., tests, procedures, and hospitalizations) and with vaccination (e.g., three doses of the vaccine at $120 per dose, wastage, supplies, and administration).42–45 Direct non-medical costs such as the patients' time and transportation were included for all strategies.

COST-EFFECTIVENESS ANALYSIS

To estimate the long-term outcomes associated with vaccination and screening, we projected the lifetime health and economic consequences for all birth cohorts of women in the first 10 years of the vaccine program. We included all birth cohorts, regardless of whether or not they received the vaccine, to capture the benefits of herd immunity in unvaccinated persons (see the Supplementary Appendix). The incremental costs and the health benefits of each vaccination strategy as compared with screening alone served as the basis for calculations of cost-effectiveness.

Strategies included HPV vaccination of 12-year-old girls and catch-up vaccination over a 5-year period for girls and women from 13 years of age to 18, 21, or 26 years of age. On the basis of rates of vaccinations among adolescents in the United States,46 we assumed that approximately 75% of the target population was covered within the first 5 years after the beginning of the program, at a coverage rate of 25% per year (Fig. 1). The efficacy of the vaccine was assumed to be lifelong and 100% against the types of HPV targeted by the vaccine among girls and women without a previous history of those infections.

All strategies included routine screening for cervical cancer with conventional or liquid-based cytologic testing, beginning in women at an average age of 20 years, according to U.S. guide-lines that recommend that screening should start 3 years after the first sexual intercourse.13,47 Abnormal results of cytologic tests were managed according to standard clinical guidelines.48 On the basis of reported patterns of cervical-cancer screening in women in the United States,49–51 we assumed that 53% of women were screened annually, 17% every 2 years, 11% every 3 years, and 14% every 5 years and that 5% were never screened. We considered scenarios in which girls who were unlikely to be vaccinated were also unlikely to be screened. We also assessed the implications of screening less frequently (every 3 or 5 years), delaying the initiation of screening (until 25 years of age), and the use of HPV DNA testing.52

To gauge the benefits of the quadrivalent vaccine against HPV-6 and HPV-11 in women, we modeled the age-specific incidence and duration of genital warts,35 including their effect on quality of life and treatment costs,36,38 and we estimated the quality-adjusted life expectancy gained and costs averted with vaccination. Similarly, we estimated the number of cases of juvenile-onset recurrent respiratory papillomatosis averted per vaccinated woman using data on the number of births per woman,53 annual incidence rates of juvenile-onset recurrent respiratory papillomatosis per live child,37 costs per case, and effects on quality of life.38,40 For both vaccines, we modeled age-specific incidence rates of HPV-16–associated and HPV-18–associated noncervical cancer among women,32 taking into account cancer-specific mortality and health-state utility weights (i.e., values from 0 to 1 indicating the quality of a person's state of health, with 0 indicating death and 1 indicating perfect health),32,39 to estimate quality-adjusted life expectancy gained and costs averted (Table 1). Vaccination was assumed to reduce the proportion of cases attributable to vaccine-targeted

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types of HPV, and we varied the efficacy on these conditions from 50% to 100% (see the Supplementary Appendix for additional details on noncervical conditions).

RESULTS

COST-EFFECTIVENESS OF VACCINATION

The routine vaccination of 12-year-old girls, in the context of current screening and assuming lifelong vaccine-induced immunity, had an incremental cost-effectiveness ratio of $43,600 per QALY gained, as compared with screening alone (Table 2). The addition of a 5-year catch-up program for girls between the ages of 13 and 18 years cost $97,300 per QALY, and extension to 21 years of age cost $120,400 per QALY. The extension of the catchup program to 26 years of age cost $152,700 per QALY, as compared with the catch-up program to 21 years of age.

Inclusion of protection against HPV-6–related and HPV-11–related genital warts reduced the cost per QALY for vaccination of preadolescent girls by 20% to $34,900, for catch-up to 18 years of age by 17% to $81,000, and for catch-up to 21 years of age by 16% to $101,300. The cost per QALY for catchup to 26 years of age was reduced by only 13%, to $133,600.

INCLUSION OF OTHER HPV-ASSOCIATED CONDITIONS

When the potential benefits associated with preventing noncervical HPV-16–related and HPV-18–related cancers and HPV-6–related and HPV-11–related juvenile-onset recurrent respiratory papillomatosis were included, cost-effectiveness ratios were reduced. The magnitude of these reductions depended on the specific outcomes that were included and on assumptions about the efficacy of the vaccine (Fig. 2). In all scenarios, the cost of vaccination of preadolescent girls remained below $50,000 per QALY, and catch-up vaccination of girls to 18 years of age remained between $50,000 and $100,000 per QALY.

EFFECT OF WANING IMMUNITY, VACCINE CROSS-PROTECTION, AND TYPE REPLACEMENT

If vaccine-induced immunity lasted only 10 years, the vaccination of preadolescent girls provided only 2% marginal improvement in the reduction in the risk of cervical cancer as compared with screening alone, and it cost $144,100 per QALY, whereas catch-up programs were more costly and less effective than screening alone (Table 3). With a completely efficacious vaccine booster at 10 years, the cost of vaccination of preadolescent girls was $83,300 per QALY, although catch-up strategies exceeded $125,000 per QALY. There were marginal improvements in cost-effectiveness when cross-protective effects were included against other high-risk types of HPV.8 Furthermore, in a separate analysis, with a 5% increase in the baseline risk of infection with high-risk types of HPV other than HPV-16 and HPV-18, the cost per QALY of vaccination of preadolescent girls increased from $43,600 to $53,000.

EFFECT OF PATTERNS OF VACCINATION AND SCREENING COVERAGE

If 5% of women in the United States were neither screened nor vaccinated, all strategies that involved a catch-up program exceeded $100,000 per QALY; catch-up to 26 years of age exceeded $200,000 per QALY (Table 4). The ratios became even less attractive when we assumed that girls who were vaccinated were preferentially screened more frequently in adulthood.

Even if all women were equally likely to be screened, the cost-effectiveness of vaccination was influenced by the frequency of screening and test protocols. With annual and biennial screening, the cost of vaccination of preadolescent girls increased to $118,200 and $45,800

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per QALY, respectively; the negative effect on the cost-effectiveness of catch-up programs was greater, with catch-up vaccination of girls and women up to 26 years of age increasing to more than $300,000 and approximately $190,000 per QALY, respectively. The cost-effectiveness ratio for the vaccination of preadolescent girls associated with initiating screening later (e.g., at 25 years of age) with the use of cytologic tests with HPV triage every 3 years, followed by combined HPV DNA testing and cytologic tests for primary screening after 35 years of age, was similar to the base case, although catchup vaccination programs for women up to 21 and 26 years of age were associated with higher cost-effectiveness ratios (see additional results in the Supplementary Appendix).

DISCUSSION

Vaccination against HPV-16 and HPV-18 is expected to be economically attractive (i.e., < $50,000 per QALY) if high coverage can be achieved in the primary target group of 12-year-old girls and if vaccine-induced immunity is lifelong. Under these conditions, if we are willing to pay $100,000 per QALY, a catch-up program for girls between 13 and 18 years of age appears to be reasonable, especially when we include the benefits of averting genital warts (with the use of the quadrivalent vaccine) or the benefits of cross-protection against other high-risk types of HPV not including HPV-16 and HPV-18 (as reported with the bivalent vaccine). Extending the catch-up program to 21 years of age is less cost-effective, but it also becomes more favorable when the potential benefits of preventing noncervical HPV-16–associated and HPV-18–associated cancers in women are included.

Extending vaccine coverage to women up to 26 years of age generally exceeds $130,000 per QALY. This result is not unexpected, since nearly 90% of women in the United States have had vaginal intercourse by 24 years of age47 and up to 30% of women may be exposed to HPV in the first year of intercourse.54 The cost of extending a catch-up program to women up to 26 years of age is less than $100,000 per QALY only in the context of 100% lifelong efficacy against other outcomes associated with HPV-16, HPV-18, HPV-6, and HPV-11 in women; these outcomes include cervical cancer, warts, other cancers, and juvenile-onset recurrent respiratory papillomatosis. The cost of extending this program is more than $200,000 per QALY when a booster is required to maintain lifelong immunity, when there are disparities in screening and vaccination coverage, and when vaccinated girls undergo frequent screening in adulthood. The benefits of vaccine in most HPV-16 and HPV-18 noncervical cancers and HPV-6 and HPV-11 juvenile-onset recurrent respiratory papillomatosis have not been shown in clinical studies.

Our results were sensitive to the duration of vaccine-induced immunity; if immunity lasted 10 years, the vaccination of preadolescent girls exceeded $140,000 per QALY, and all catch-up strategies were less cost-effective than screening alone. Although immunologic data have provided support for a strong initial immune response with antibody levels persisting at a level higher than the level after natural infection,9›55›56 observations in published reports are limited to 5 years after vaccination. With partial natural immunity to type-specific infection, if a vaccinated girl loses vaccine-induced protection and becomes susceptible at a later age when the risk of cancer may be higher, an increased risk of cervical cancer is plausible. There are no empirical data to show whether reinfection or reactivation of a previous infection predominates in older women; as previously described,17 which one of these predominates will influence the implications of waning vaccine protection. There are other important uncertainties. Although HPV infections may be independent from one another,56 our exploratory analysis showed that replacement of the vaccine-targeted types of HPV with other high-risk types could be influential. Vaccination against HPV may also alter sexual behavior in the population or lead to a misperception that screening is no longer

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necessary. These uncertainties highlight the priorities for surveillance of epidemiologic characteristics and behaviors after vaccination against HPV.

Our results of vaccinating preadolescent girls were consistent with those of other studies.[17–22,57,58] Elbasha et al.[21] reported that the cost of a catchup program in women up to 24 years of age was less than $5,000 per QALY; none of our strategies had a cost-effectiveness ratio this low, and the cost of a catch-up program in women up to 26 years of age generally exceeded $100,000 per QALY. Differences in assumptions have been summarized in several review articles.[59–61] Our findings, which were consistent with those of others,[20,22] were that high vaccination coverage warranted modification of screening protocols and that the cost-effectiveness of vaccination was enhanced with less frequent screening with more sensitive tests and beginning at later ages.

Our analysis has important limitations. Data on sexual behavior were primarily based on population averages from large surveys, and there were limited data on type-specific HPV transmission according to age and sex. By means of a model-fitting process, we estimated probabilities of transmission that were higher than those of some other analyses[62,63]; as better data become available, the estimation of these variables may be refined. Other limitations of the data included the incidence, mortality, and quality of life associated with noncervical HPV-related cancers, the long-term efficacy of the vaccine against cervical lesions and warts, and the efficacy of the vaccine against non-cervical cancers. As with all model-based analyses, there are trade-offs with regard to the choice of model structure; we used two different modeling techniques to try to best capture the features of HPV infection and cervical carcinogenesis that were most relevant to the key policy questions. The complexities that are introduced with the use of multiple models should be explored further.[24]

A decision-analytic approach allows for acknowledgment of uncertainty while informing decisions that need to be made now. Accordingly, we emphasized broad qualitative themes that we found to be consistent throughout a range of assumptions. The cost-effectiveness of HPV vaccination in the United States will likely be optimized by achieving universal coverage in young adolescent girls and targeting initial catch-up efforts to girls and women younger than 21 years of age. Optimal synergies between vaccination and screening will involve revisions to current screening practice. Priorities for empirical data collection include surveillance to understand the HPV type-specific epidemiologic factors and screening behavior in vaccinated populations, the duration of vaccine-induced protection, and the long-term impact on other HPV-related conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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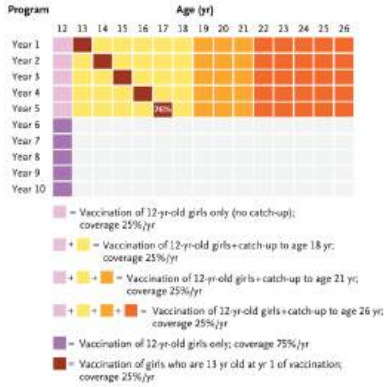


Figure 1. Vaccination Coverage

Pink boxes indicate vaccination of preadolescent 12-year-old girls at a coverage rate of 25% per year for the first 5 years of the vaccination program; purple boxes indicate a coverage rate of 75% in years 6 to 10 of the vaccination program. Without a catch-up program, each birth cohort of 12-year-olds had no future opportunities for vaccination beyond a single year. Yellow, light-orange, and dark-orange boxes indicate catch-up vaccination of girls and women from age 13 up to 18, 21, or 26 years of age, which occurred over a 5-year period at 25% coverage per year. Therefore, an additional 25% of the initial cohort of 12-year-old girls who were not vaccinated in the first year had another opportunity to receive the vaccine in the second year of the program, when they were 13 years old; such opportunities continued through program year 5. Brown boxes show catch-up vaccination in the initial cohort of 13-year-old girls. In year 1 of the vaccination program, 25% of the 13-year-old girls were assumed to be covered; in year 2, among the 75% of 13-year-olds who were not vaccinated in year 1, 25% would be covered when they were 14 years old. At the end of year 5, 76% of the original cohort of 13-year-olds was covered. The number of opportunities for vaccination depended on the specific catch-up strategy; for example, a 16-year-old in the first year of the program would have only three chances of receiving the vaccine in a catch-up program up to 18 years of age, since she would be older than 18 years of age in program year 4.

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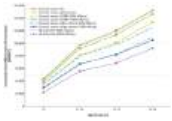


Figure 2. Effect of Inclusion of Other Health Conditions on the Cost-Effectiveness of Vaccination Strategies

The solid lines represent analyses in which the efficacy of the vaccine against human papillomavirus (HPV) was assumed to be 100% among girls and women without a previous history of type-specific infection (for all conditions). The dashed lines represent analyses in which the efficacy of the vaccine was assumed to be 50% (only for cancers other than cervical cancer and juvenile-onset recurrent respiratory papillomatosis [JORRP]; the efficacy remained 100% for cervical cancer and genital warts) among girls and women without a previous history of type-specific infection. In all analyses, the efficacy of the vaccine was assumed to be 0% among persons with a previous type-specific infection or infections. Including the potential benefits of the vaccine against noncervical HPV-16–related and HPV-18–related cancers, HPV-6–related and HPV-11–related JORRP, or both reduced the cost-effectiveness ratios, but the magnitude of the reduction depended on the specific outcomes included and the assumptions about efficacy. For instance, including other cancers reduced the cost-effectiveness ratios from 18% to 30% depending on the efficacy of the vaccine, whereas including JORRP had less of an effect. Under all assumptions, the cost of vaccination of preadolescent girls (i.e., 12-year-old girls) remained below $50,000 per quality-adjusted life-year (QALY), and the cost of catch-up vaccination of girls to 18 years of age was between $50,000 and $100,000 per QALY. The cost of catch-up vaccination of girls and women to 21 years of age decreased below $100,000 per QALY when other cancers or all outcomes were included, and the cost of catch-up vaccination to 26 years of age exceeded $100,000 per QALY, unless all outcomes were included with a vaccine efficacy of 100% for all conditions.

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Table 1

Values for HPV-Related Health Conditions in the Model.*

Variable	Values	Reference
Cervical cancer		
Incidence (no./100,000 women)†	4.2–62.8	
Five-year survival (%)‡	16.5–92.0	National Cancer Institute32
Quality-of-life adjustment§	0.48–0.76	Myers et al.,36 Gold et al.39
Cases attributable to HPV-16 and HPV-18 (%)	70.0	Parkin and Bray2
Cost per case ($)¶	26,540–45,540	Goldie et al.33
Vulvar cancer		
Incidence (no./100,000 women)	0.2–24.9	National Cancer Institute32
Five-year survival (%)	77.8	National Cancer Institute32
Quality-of-life adjustment§	0.68	Gold et al.39
Cases attributable to HPV-16 and HPV-18 (%)	32.0	Parkin and Bray2
Cost per case ($)¶	20,430	Hu and Goldie38
Vaginal cancer		
Incidence (no./100,000 women)	0.1–6.0	National Cancer Institute32
Five-year survival (%)	55.7	National Cancer Institute32
Quality-of-life adjustment§	0.68	Gold et al.39
Cases attributable to HPV-16 and HPV-18 (%)	32.0	Parkin and Bray2
Cost per case ($)¶	23,440	Hu and Goldie38
Anal cancer		
Incidence (no./100,000 women)	0.0–5.6	National Cancer Institute32
Five-year survival (%)	66.2	National Cancer Institute32
Quality-of-life adjustment§	0.68	Gold et al.39
Cases attributable to HPV-16 and HPV-18 (%)	82.8	Parkin and Bray2
Cost per case ($)¶	31,300	Hu and Goldie38
Oral cancer		
Incidence (no./100,000 women)	0.2–13.9	National Cancer Institute32
Five-year survival (%)	62.6	National Cancer Institute32
Quality-of-life adjustment§	0.68	
Cases attributable to HPV-16 and HPV-18 (%)	2.9	Parkin and Bray2
Cost per case ($)¶	37,370	Hu and Goldie38
Oropharyngeal cancer		
Incidence (no./100,000 women)	0.0–1.1	National Cancer Institute32
Five-year survival (%)	62.6	National Cancer Institute32
Quality-of-life adjustment§	0.68	
Cases attributable to HPV-16 and HPV-18 (%)	10.7	Parkin and Bray2
Cost per case ($)¶	37,370	Hu and Goldie38
Genital warts		

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Variable	Values	Reference
Prevalence (no./1000 women)	0.07–6.20	Insinga et al.35
Quality-of-life adjustment§	0.91	Insinga et al.,35 Myers et al.36
Cases attributable to HPV-6 and HPV-11 (%)	100	Lacey et al.10
Cost per case ($)¶	430	Hu and Goldie38
Juvenile-onset recurrent respiratory papillomatosis		
Incidence (no./100,000 children 0–14 yr old)	4.30	Derkay37
Quality-of-life adjustment§	0.69	Bishai et al.40
Cases attributable to HPV-6 and HPV-11 (%)	100	Lacey et al.10
Cost per case ($)¶	62,010	Hu and Goldie38

* Ranges represent age-specific values, and rates are annual rates unless otherwise noted. HPV denotes human papillomavirus.

† Incidence rates for cervical cancer were generated by the calibrated stochastic model in the absence of screening or vaccination (i.e., natural history).

‡ The 5-year survival for cervical cancer varied according to the stage (i.e., 92.0% for local, 55.7% for regional, and 16.5% for distant disease).

§ The quality-of-life adjustment assumed a health-state utility weight of 0 (death) to 1 (perfect health). The health-state utility weight for cervical cancer varied according to the stage: 0.76 for local cancer, 0.67 for regional cancer for a period of 5 years, and 0.48 for distant cancer over the lifetime with disease. For noncervical cancers, we assumed an average health-state utility weight of 0.68 over the lifetime with disease in order to reflect a weighted average of stage-specific utility weights and distribution of disease according to stage. For genital warts, we assumed a health-state utility weight of 0.91 over 3 months. All disease-specific utility weights were multiplied to baseline age-specific utility weights in order to estimate the overall utility weight (data are from Fryback et al.41).

¶ The cost per case is expressed in 2006 U.S. dollars and represents the average discounted lifetime costs of a new case of disease, including direct medical costs (i.e., the cost of procedures, hospitalizations, and office visits). The costs of treatment of cervical cancer varied according to stage (e.g., $26,540 for local, $28,430 for regional, and $45,540 for distant disease) and included direct nonmedical costs such as the patients' time and transportation.

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Table 2

Cost-Effectiveness of Vaccination of Preadolescent Girls and Temporary Catch-Up Programs.*

Strategy†	Base Case‡	With Outcomes Related to HPV-6 and HPV-11 Genital Warts§
		$/QALY
Screening only¶	—	—
Vaccination (age 12 yr)	43,600	34,900
Vaccination (age 12 yr) plus catch-up vaccination (age 13–18 yr)	97,300	81,000
Vaccination (age 12 yr) plus catch-up vaccination (age 13–21 yr)	120,400	101,300
Vaccination (age 12 yr) plus catch-up vaccination (age 13–26 yr)	152,700	133,600

* The values represent incremental cost-effectiveness ratios (i.e., the additional cost divided by the additional health benefit compared with the next-less-costly strategy) expressed as cost per quality-adjusted life-year ($/QALY). All costs are expressed in 2006 U.S. dollars. HPV denotes human papillomavirus.

† All strategies included current cytologic screening (see the Methods section).

‡ The base-case analysis reflected the outcomes related to cervical cancer only.

§ The analysis included outcomes related to cervical cancer and HPV-6–associated and HPV-11–associated genital warts in girls and women.

¶ Since screening only is the baseline strategy, it is not associated with an incremental cost-effectiveness ratio.

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Table 3

Effect of Uncertain Vaccine Properties on Cost-Effectiveness.*

Strategy†	Base Case‡	Waning Immunity at 10 Yr§	Booster at 10 Yr¶	Inclusion of Cross-Protection against Other High-Risk Types of HPV‖
		$/QALY		
Screening only**	—	—	—	—
Vaccination (age 12 yr)	43,600	144,100	83,300	33,700
Vaccination (age 12 yr) plus catch-up vaccination (age 13–18 yr)	97,300	Not cost-effective	140,700	79,300
Vaccination (age 12 yr) plus catch-up vaccination (age 13–21 yr)	120,400	Not cost-effective	185,400	102,200
Vaccination (age 12 yr) plus catch-up vaccination (age 13–26 yr)	152,700	Not cost-effective	233,500	129,500

* The values represent incremental cost-effectiveness ratios (i.e., the additional cost divided by the additional health benefit compared with the next-less-costly strategy) expressed as cost per quality-adjusted life-year ($/QALY). A strategy that is not cost-effective is more costly and less effective than another strategy. All costs are expressed in 2006 U.S. dollars. HPV denotes human papillomavirus.

† All strategies included current cytologic screening (see the Methods section).

‡ The base-case analysis reflected the outcomes related to cervical cancer only.

§ The analysis assumed full vaccine-induced protection up to 10 years, after which protection waned completely.

¶ The analysis assumed a vaccine booster was administered to all previously vaccinated persons 10 years after initial vaccination and provided lifelong protection. The booster was assumed to cost $250 per vaccinated person (including the cost of the vaccine dose, supplies, wastage, administration, and patients' time and transportation, as well as an additional cost for the booster campaign and outreach efforts).

‖ The efficacy of the vaccine against other high-risk types of HPV (i.e., other than HPV-16 and HPV-18) was assumed to be 27.1%; data are from Paavonen et al.8

** Since screening only is the baseline strategy, it is not associated with an incremental cost-effectiveness ratio.

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Table 4

Effect of Disparities in Vaccination and Screening Coverage and Revised Cervical-Cancer Screening Policies on Cost-Effectiveness.*

Strategy	Base Case†	Vaccine Coverage		Screening Policy		
		Only Women Who Will Be Screened‡	Only Women Who Will Be Screened Frequently§	Cytologic Screening (1 yr)¶	Cytologic Screening (2 yr)¶	Revised Screening (3 yr)‖
			$/QALY			
Screening only**	—	—	—	—	—	—
Vaccination (age 12 yr)	43,600	47,900	106,000	118,200	45,800	40,900
Vaccination (age 12 yr) plus catch-up vaccination (13–18 yr)	97,300	121,900	136,300	186,700	102,400	103,500
Vaccination (age 12 yr) plus catch-up vaccination (13–21 yr)	120,400	153,300	172,400	250,600	120,600	128,700
Vaccination (age 12 yr) plus catch-up vaccination (13–26 yr)	152,700	204,700	231,000	324,200	189,700	185,400

* The values represent incremental cost-effectiveness ratios (i.e., the additional cost divided by the additional health benefit compared with the next-less-costly strategy), expressed as the cost per quality-adjusted life-year ($/QALY). All analyses reflect outcomes related to cervical cancer only. All costs are expressed in 2006 U.S. dollars. HPV denotes human papillomavirus.

† The base-case analysis included current cytologic screening (see the Methods section).

‡ The analysis assumed that women who were never screened were also not vaccinated.

§ The analysis assumed that women who were screened less frequently (i.e., every 5 years or never) were also not vaccinated.

¶ The analysis assumed the base-case screening test and age for initiation of screening, but the screening interval was changed to every 1 or 2 years, which is consistent with current screening guidelines.

‖ The analysis assumed cytologic screening with HPV DNA testing as triage for equivocal results starting at 25 years of age, with a switch to combined cytologic and HPV DNA testing starting at 35 years of age.

** Since screening only is the baseline strategy, it is not associated with an incremental cost-effectiveness ratio.

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IN THE HON'BLE HIGH COURT OF DELHI
AT NEW DELHI
WRIT PETITION (CIVIL) NO_____OF 2026
IN THE MATTER OF A PUBLIC INTEREST LITIGATION

IN THE MATTER OF:

Dr. Sujata Mittal and Anr. ...Petitioner(s)

Vs.

Union of India and Others ...Respondent(s)

APPLICATION ON THE BEHALF OF THE PETITIONERS UNDER SECTION 151 OF THE CODE OF CIVIL PROCEDURE,1908, SEEKING INTERIM STAY.

MOST RESPECTFULLY SHOWETH:-

1. That the present Writ Petition is being filed in public interest under Article 226 of the Constitution of India, seeking urgent intervention of this Hon'ble Court in relation to the nationwide rollout of the HPV vaccine under the Universal Immunisation Programme (UIP), raising concerns of violation of fundamental rights under Articles 14, 19 and 21 of the Constitution of India, in the absence of adequate long-term safety data, informed consent protocols, and pharmacovigilance and adverse event surveillance mechanisms, thereby violating the right to life and more particularly bodily integrity, and personal autonomy of the young girls of India.

2. The contents of the foregoing Writ petition may be read as part and parcel of the present application as the same are not repeated for the sake of brevity.

3. That the Petitioners submit that until a comprehensive, independent scientific review of the long-term safety data, pharmacovigilance reports, adverse event surveillance data, and India-specific clinical efficacy data pertaining to the HPV vaccine is conducted and publicly disclosed, and until adequate informed consent protocols and grievance redressal mechanisms are put in place, the Respondents may be directed to forthwith stay any further mass administration of the HPV vaccine under the Universal Immunisation Programme, pending the outcome of the present petition.

4. That irreparable loss and prejudice is likely to be caused if the instant application is not allowed, however, no such prejudice is likely to be caused to the Respondents.

5. That the instant Application is bonafide and in the interest of justice and no prejudice will be caused to anybody if the present Application is allowed.