REVIEW

The Present Scenario of Cervical Cancer Control and HPV Epidemiology in India: an Outline

J Giftson Senapathy[1], P Umadevi[1]*, PS Kannika[2]

Abstract

Objective: To give a clear picture with epidemiological evidence about the present scenario of cervical cancer control and HPV in India. Design: Review of published studies, concentrating on recent systematic reviews, meta-analyses and large prospective studies. Conclusions and recommendations: Cervical cancer is unique among cancers in that it can largely be prevented through screening and removal of precursor lesions. It is the second most common cancer among women worldwide and is the most common malignancy in developing countries, particularly in India. Nowadays, cervical screening for women is necessary because there are no signs and symptoms of cervical precancers. The establishment of a prevention program is urgently required considering both screening and vaccination. But most women in India do not have access to effective screening programmes. It has been estimated that in India, even with a major effort to expand cytology services, it will not be possible to screen even one-fourth of the population once in a lifetime in the near future. New HPV vaccines will also help prevent HPV infection and the precancerous changes that lead to cervical cancer. The focus on detection and prevention of cervical cancer must be emphasized in a highly populated country like India to prevent its extensive spread.

Keywords: Cervical cancer - screening - risk factors - human papilloma virus - vaccine - India

Asian Pacific J Cancer Prev, **12**, 1107-1115

Introduction

Cancer is perhaps the most progressive and devastating disease posing a threat of mortality to the entire world despite significant advances in medical technology for its diagnosis and treatment. It is estimated that by the year 2020 there will be almost 20 million new cases. Worryingly, it is not only in the number of new cases that will increase but also the proportion of new cases from the developing countries like India will also rise to around 70%. The magnitude of the problem of cancer in the Indian Sub-Continent is alarming (Rao and Ganesh, 1998). Though the cancer incidence rate in India is less than that of the Western countries but due to the large population size, number of cases is more prevalent at any time (Krishnan and Sankaranarayanan, 1991).

The most common cancers among females are cervix, breast, ovary, oesophagus and mouth. Of this, cervical cancer is the second most common cancer among women worldwide after breast cancer. According to the WHO report, globally, cervical cancer comprises 12% of all cancers in women and it is the leading gynecological malignancy in the world (Kamalesh et al., 2008). In many developing countries, it is the most common cancer among women where 85% of the estimated 493 000 new cases and 273 000 deaths in 2002 occurred worldwide. It is an important public health problem for adult women in developing countries (Parkin et al., 2002; Ferlay et al., 2001). The risk of cervical cancer remains high in many developing countries mostly due to the lack or inefficiency of existing prevention programmes. This review attempts to give a brief picture about the scenario of cervical cancer prevention and HPV epidemiology in India

Incidence and Mortality Patterns in India

India has a population of approximately 1.2 billion and accounts for a significant burden of cervical cancer in the Indian subcontinent. There is an estimated annual global incidence of 500 000 cancers, in that India contributes 100 000 i.e., one-fifth of the world burden (Shanta, 2003). A total of 4304 cervical cancer cases were registered during 1982-89 in the Chennai registry, India. In 1990, twenty percent of all female deaths from cancer in India, were from cervical cancer, amounting to an estimated 6 100 deaths (Gajalakshmi et al., 2003). In 1996, cervical cancer accounted for 247 000 deaths in women. Approximately 20 000 new cases were detected in India, in the year 2000 (Mandal et al., 2003). Recently a report says that there are an estimated 1.32 lakh new cases and 74 000 deaths annually in India (Priyanka, 2009). The number of cervical cancer deaths in women in India is projected to increase to

*[1]SDepartment of Biotechnology, School of Biotechnology and Health Sciences, Karunya University, [2]Department of Biotechnology, Dr. NGP Arts and Science College, Coimbatore, Tamilnadu, India *For correspondence : umadevipongiya@rediffmail.com*

79 000 by the year 2010. Particularly, in Southern India, carcinoma of the uterine cervix is the most common form of cancer in females (Shanta 2003).

Information on cancer patterns and burden in India is based on the projections from 18 population-based cancer registries covering approximately 4% of the population, including three rural registries in different regions. Age-standardized cervical cancer incidence rates range from 9 to 40 per 100 000 women in various regions of India (Curado et al., 2007; Cancer Atlas, 2008). The estimated age-standardized cervical cancer incidence and mortality rates around 2002 were 30.7 and 17.8 per 100 000 women respectively. The peak incidence was observed in older women 70 years of age (Ferlay et al., 2004). The impact of control measures in India will substantially reduce the global burden. The number of maternal deaths and cervical cancer cases is almost equal in India (WHO, 2008). There is considerable awareness, advocacy and investment to reduce maternal deaths (undoubtedly an extremely justifiable investment) among policy makers, governments, professional societies (including the Federation of Obstetric & Gynaecology Societies of India (FOGSI), perhaps the largest professional organization in the world), social organizations and women's movements. It is paradoxical that there is very limited awareness on cervical cancer as a threat to the health of middle-aged women in the most productive period of their life.

Risk factors

A risk factor is something that increases your chances of developing a disease or condition. Epidemiological studies have identified a number of risk factors such as infection with certain oncogenic types of human papillomaviruses (HPV), sexual intercourse at an early age, multiple sexual partners, multiparity, long-term oral contraceptive use, tobacco smoking, low socio-economic status, infection with Chlamydia trachamatis, micronutrient deficiency, and a diet deficient in vegetables and fruits, that contribute to the development of cervical cancer (IARC Working Group, 1995; Walboomers et al., 1995; Ferenczy and France 2002). Infection with one or more of the oncogenic HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 is considered to be a necessary cause for cervical neoplasia (IARC Working Group, 1995).

HPV Epidemiology in Different Parts of India

The available information on HPV epidemiology is mostly based on research studies addressing cervical screening and HPV infection in selected locations in India. A study on the prevalence of highrisk HPV (HR-HPV) infection among apparently healthy populations in various regions of India reported that, the HR-HPV prevalence rates varied between 7–13%, but were mostly above 10%. The most common HPV types reported were (in descending order) HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 (Franceschi et al., 2005; Clifford et al., 2005; Sankaranarayanan et al., 2004 & 2005; Sowjanya et al., 2005; Laikangbam et al., 2007). Overall HPV prevalence in India was similar to the high-risk areas in Latin America, but lower than that observed in some parts of sub-Saharan Africa (Clifford et al., 2005).

In a hospital-based case-control study, 27.7% of 210 normal women were positive for any HPV type and 21.7% were positive for HR-HPV types. In a population-based study involving 651 women in Ballabgarh, a rural area near Delhi, 7.1% were positive for HR-HPV using polymerase chain reaction (PCR) line-blot assay. A population-based, cross-sectional survey in married women aged 16–59 years was conducted in rural Dindigul district (Franceschi et al., 2003 & 2005). The prevalence of any HPV type was 16.9% in the general population, of which 14.0% (252/1,799) were among women without cervical abnormalities and 73.9% (68/92) among those with cytological abnormalities. Age-standardized proportions were 17.5%, 15.2% and 64.9%, respectively. The prevalence of HR-HPV infection was 12.5%, with multiple HPV types detected in one-fifth of the infected women (Franceschi et al., 2005; Clifford et al., 2005). Among 27,212 women aged 30–59 years in Osmanabad district, 10.4% of the women were positive for HR-HPV DNA [by Hybrid Capture ® 2 (HC2), Qiagen Gaithersburg, Inc., MD, USA (previously Digene Corp.)], 12% of whom had cervical intraepithelial neoplasia (CIN) lesions of grade 2–3 or invasive cancer. In a multi-centre, cross-sectional study that involved 18,085 women aged 25–65 years recruited from three cities in India, evaluated the accuracy of HPV testing (by HC2) in detecting CIN2-3 lesions in which 7% were HR-HPV positive and 12.8% of these had CIN2-3 lesions or invasive cancer (Sanakaranarayanan et al., 2005 & 2004).

Unlike most populations in developed countries, HPV prevalence was constant across age groups in India, with no clear peak in young women. In the Osmanabad district study, the prevalence of HR-HPV types in the 30–39, 40–49 and 50–59 age groups were 9.8%, 10.4% and 12.2%, respectively. In the multicentre cross-sectional study in India, these were 7.0%, 6.8% and 7.5%, respectively. The population-based study in Dindigul, which included a broad age range of women 16–25 years, did not find any peak prevalence in the younger age group (Franceschi et al., 2005; Clifford et al., 2005; Sanakaranarayanan et al., 2005). Low clearance of incident infections, frequent re-infection/reactivation, underrepresentation of teenagers in the study samples and sexual behavioural patterns in the population may be responsible for the constant, steady prevalence of HPV infection in different age groups in India. It is also notable that all studies are restricted in enrolment to married women due to the cultural taboo of genital tract sampling of an unmarried woman. Cultural influences specific to rural India might also factor into the lack of a peak in HPV prevalence when restricting analyses to married women. Based on data from the National Family Health Survey of India (2005–2006), there was a noticeable gap in the age at marriage between women and men, with 52.5% of rural Indian women reporting marriage before age 18, while only 36.5% of men reported marriage before age 21 (IIPS, 2008). Furthermore, there was greater age discordance in married couples (22% of men are older than their wives by 6 years or more) and this was associated with an increased probability of

the husband reporting extramarital sexual relationships (Schensul et al., 2006).

Few studies have addressed the prevalence of pre-marital sexual contacts in rural India, though formative research conducted in rural Andhra Pradesh indicates that this may be a significant factor influencing age at first HPV exposure (Clifford et al., 2003). In a study in Madurai in South India, HPV DNA was detected in 70% of the 43 samples analyzed: HPV-16 in 23 cases (53%), HPV-18 in four cases (13.3%), and HPV-33 in one case (3.3%) (Munirajan et al., 1998). A hospital based case-control study in Chennai found 23 different HPV types among 190 of 191 cervical cancer cases. HPV infection of any type was associated with a 498-fold increased risk for cervical cancer in this study; those infected with HPV-18 had a higher risk for cervical cancer compared to women infected with HPV-16, multiple infections did not increase risk. Illiteracy, no toilet or running water inside the house, not washing genitals after sexual intercourse, age at first sexual intercourse <15 years, more than two lifetime sexual partners and widowhood were associated with increased risk of cervical cancer (Franceschi et al., 2003). In a study of 106 cervical cancer biopsy specimens from north India, 98.1% were positive for HR-HPV types among which 12 different HPV types were detected (Bhatla et al., 2006). Eighteen HPV types were identified in cervical cancer specimens in a study in Vellore (Peedicayil et al., 2006). Furthermore, in a study evaluating 59 cervical cancer specimens from Kolkata and 34 from Nagpur, HPV DNA was detected in 72 cases. Theoretically, an HPV vaccine with 100% efficacy in preventing HPV-16 and 18 infections could potentially reduce the cervical cancer burden by more than 60%, assuming 100% coverage.

Cervical Cancer Screening in India

Cervical cancer is preventable, but most women in poorer countries do not have access to effective screening programmes. There are no organized screening programs in any province or region of India. Screening of asymptomatic women is practically absent, even among otherwise well-organized health care programs of the industrial and military sectors (Gheit et al., 2009). Resource constraint has been a major hurdle in organizing screening programs. It has been estimated that in India, even with a major effort to expand cytology services, it will not be possible to screen even one-fourth of the population once in a lifetime in the near future (Directorate General of Health Services, 1984, Stjernsward et al., 1987).

Conventional cytology is offered sporadically to women in selected urban areas attending health services for other reasons, but not as routine screening of asymptomatic women. According to a WHO Health Survey in 2002, 2.6% of 4 586 women aged 18–69 years, ever had a Pap smear (WHO, 2008). It is estimated that less than 1.5 million smears are opportunistically taken annually. In recent years, HPV DNA testing (by HC2) is increasingly used in the private sector, though it is likely that less than 50 000 HPV tests are carried out annually.

The difficulties in implementing an organized cervical cytology screening in India and other low-resource countries have prompted several Indian researchers to evaluate affordable and effective alternative screening approaches to facilitate evolution and implementation of cost-effective screening in due course (Sankaranarayanan et al., 2003). These studies are briefly reviewed. The accuracy of conventional cytology, HPV testing, visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI) in the early detection of CIN2-3 lesions has been addressed in several cross-sectional studies (Sanakaranarayanan et al., 2004; Parashari et al., 200; Londhe et al., 1997; Basu et al., 2003).

In a cost-effectiveness study of different cervical screening approaches in India and other developing countries, screening women once a lifetime, at the age of 35 years, with a one- or two-visit screening strategy involving VIA or HPV testing reduced the lifetime risk of cancer by approximately 25–36% and cost less than 500 US dollars per year of life saved. The relative cancer risk declined by an additional 40% with two screenings (at 35 and 40 years of age), resulting in a cost per year of life saved that was less than each country's per capita gross domestic product-avery cost effective result (Goldie et al., 2005). The findings and experiences from the Indian screening studies (Sankaranarayanan et al., 2005; Sanakaranarayanan et al., 2004; Arbyn et al., 2006; Sankaranarayanan et al., 2007, Legood et al., 2005) have substantially contributed to the development of guidelines and training manuals for global use (ACCP, 2004; WHO, 2006, Sankaranarayanan and Wesley, 2003; Sellors and Sankaranarayanan, 2003). Of all the screening tests available, the three main cervical cancer screening procedures commonly employed in India were Papanicolaou smears (Pap smears), visual inspection with acetic acid (VIA) and HPV testing.

Papanicolaou smears

Papanicolaou (Pap) smears are used to screen for cervical cancer. "Screening for cancer" means looking for cancer before a person has symptoms. To perform a Pap smear, doctors use a swab during an internal examination of the vagina to take a sample of cells from the cervix to look at under a microscope. Having a Pap smear every 1 to 3 years helps prevent cervical cancer by finding it at early, treatable stages. It is also possible to test for HPV, and experts are trying to determine the best way to combine HPV and Pap tests in cervical cancer screening. Some doctors test women for HPV only if the Pap smear shows abnormal cells that are not clearly cancerous. Other doctors use both tests together for all women older than 30 years, because cervical cancer is very rare before age 30 years (Kim et al., 2009) .

There was a reduction in the health budget from 7.02% in 1985–1986 to 4.97% in 2003– 2004, and the expenditure on health has stagnated at 0.9% of the GDP 1 (Gross Domestic Product) with the priorities being population control and contraception, prevention of infant and maternal mortality, universal immunization, and communicable diseases. It was estimated in 1986 that if the available resources for cytology had been increased

twelve-fold it would be sufficient to administer one cervical smear examination to 25% of the population at risk once in their lifetime (WHO, 1986). Hence it was accepted that the Papanicolaou smear test could not be used as a public health strategy for cervical cancer in India.

Visual Inspection with acetic acid (VIA)

Cervical cancer prevention efforts worldwide have so far entirely focused on cytology screening. The difficulties and resource constraints in introducing cervical cytology screening programs and the sub-optimal performance of Pap smear screening in less developed countries have encouraged the evaluation of visual inspection with 3–5% acetic acid (VIA) as an alternative screening method. VIA meets the criteria of a good screening test, the test itself is simple to administer, and the assessment results are immediately available. VIA involves visually examining the cervix for lesions with the naked eye no magnification after the application of a 3-5% acetic acid wash (Sankaranarayanan et al., 2001).

In several studies, VIA had an acceptable sensitivity in detecting cervical intraepithelial neoplasia (CIN). Model-based studies suggest that low-intensity, single-round of VIA screening once a lifetime is a cost effective method to reduce disease burden (Goldie et al., 2005; Goldie et al., 2001; Mandelblatt et al., 2002; Sankaranarayanan et al., 2004; Sankaranaraynan et al., 2000). The Christian Fellowship Community Health Centre, India, and the International Agency for Research on Cancer (IARC) of WHO, France, jointly did a cluster randomized trial to assess the efficacy of VIA screening to reduce cervical cancer incidence and mortality in a high-risk population in India. The results, after 7 years from the beginning of the screening, in terms of reduction in cervical cancer incidence and mortality, were positive with a significant decline in the cervical cancer burden (Denny et al., 2005).

VIA involves naked eye inspection of the uterine cervix after application of dilute acetic acid to visualize definite, opaque acetowhite lesions close to the squamocolumnar junction. VIA can be provided by a variety of personnel such as trained nurses, midwives and health workers. Recent studies indicate that it has a sensitivity ranging from 70 to 85% in detecting high-grade cervical intraepithelial neoplasia (CIN 2–3) and invasive cancer; its specificity ranges from 67 to 85% (University of Zimbabwe, 1999; Belinson et al., 2001; Sankaranarayanan et al., 2003).

In a randomized controlled clinical trial conducted in Dindigul District, Tamil Nadu, India, to evaluate the effectiveness of VIA screening in reducing cervical cancer incidence and mortality, a high incidence of cervical cancer is observed (Sanakaranarayanan et al., 2000). The study also indicates that, women accept screening with VIA by nurses (as well as colposcopy and cryotherapy by nurses), and that a moderate level of compliance with screening and treatment can be reached through appropriate service delivery mechanisms including health education activities, personal invitations, clinics in proximity to the target population, and by testing, diagnosis and treatment in the same session.

HPV Testing

HPV testing is employed for the detection of specific high risk HPV types. In 2000, Sankaranarayanan et al., employed HPV testing in a cluster-randomised controlled trial on HPV screening for cervical cancer in rural India particularly in the Osmanabad district in the state of Maharashtra. They reported that, HPV testing was the most objective and reproducible of all cervical screening tests and was less demanding in terms of training and quality assurance. In low-resource settings with no capacity for colposcopy and histopathological analysis (e.g., many countries in sub-Saharan Africa), HPV-positive women without clinical evidence of invasive cancer could receive immediate treatment, such as cryotherapy (Denny et al., 2005). However, since most HPV infections in young women regress rapidly without causing clinically significant disease, such an approach raises a legitimate concern. Hence, HPV testing should not be used for primary screening of women under 30 years of age. A drawback to HPV testing is that it is more expensive ($20 to $30 per test, in U.S. dollars) and time-consuming than other screening tests, and it requires a sophisticated laboratory infrastructure. The HPV test costs around Rs.1250 per test in private medical centres in India. A simple, affordable, and accurate HPV test (careHPV test, Qiagen) that provides results within 3 hours was evaluated in China. The careHPV test had higher sensitivity than VIA (90.2% vs. 41.4%) but a lower specificity (84.2% vs. 94.5%) (Qiao et al., 2008). The careHPV test is expected to be commercially available in India and developing countries in the near future.

HPV Vaccines

Recent data from All India Institute of Medical Sciences (AIIMS) in New Delhi, India states that although a wide spectrum of HPV is seen across India, HPV-16 and HPV-18 are the most common types and a vaccine targeting these types could eliminate 75% of cervical cancers in the country. HPV vaccines have been developed and vaccination, if done before the person becomes sexually active, would offer great protection. HPV vaccines like Gardasil and Cervarix offer protection against HPV-16 and -18 and are given in three doses over a six-month period. In 2008, the worldwide sales of Gardasil and Cervarix were worth about $1.4 billion and $232 million respectively. Gardasil also offers protection against HPV-6 and -11, which cause genital warts in males (Priyanka, 2009). Although Cervarix and Gardasil protect against infection with HPV types 16 and 18, these vaccines do not protect against HPV types found in approximately 30% of cervical cancers (Cervical cancer; Fact Sheet, 2007). Although HPV vaccination is a promising control option, it will take several decades to establish its effect on cervical cancer burden and the vaccine costs are currently prohibitive. Timely implementation of an affordable and effective screening strategy in developing countries is thus crucial, while waiting for further improvements in HPV testing, vaccine technology, costs, and its widespread use. The prospects for HPV vaccination in public health services have to be judged in the backdrop of the realities

for intensely advocated and essential Expanded Program of Immunization (EPI) vaccines, which are perceived as extremely high priority vaccines. Coverage for three doses of the diphtheria and tetanus toxoids and pertussis (DTP3) and of polio vaccines for the year 2005 was estimated at 60% by the World Health Organization-United Nations Children's Fund (WHO-UNICEF) and 90% by national estimates; coverage for hepatitis B vaccine for the same year was barely 8% by WHO estimates and 68% by national estimates. The low coverage for these vaccines is surprising given the high awareness among parents, health care providers and policy makers, state funding, availability of infrastructure for storage and delivery and the fact that childhood immunization is relatively more successful among the public health programs in India. India reported 2 587 cases of tetanus and 676 cases of polio in 2006 (WHO, 2008).

The HPV vaccine is not yet licensed or marketed in India, but a major obstacle to its introduction is likely to be its prohibitive cost. To illustrate the magnitude of the cost of an HPV vaccine, the current costs of three doses of HPV vaccines in Europe are 150 times higher than the entire cost of the EPI vaccines in India. Research into less expensive second-generation prophylactic HPV vaccines is promising. Subunit (capsomere) vaccines can be more cheaply manufactured in E.coli and require no cold-chain. Monovalent vaccines, based on the L2 protein, offer broader protection across the genotype spectrum. Needle-free delivery systems are also under development. India's biotechnology sector is leading the way in this research by producing the first good manufacturing practices (GMP)-grade L2 and capsomere vaccines in collaboration with international researchers. There are certain unique socio-cultural issues associated with the HPV vaccine because it targets a sexually transmitted infection (STI) and primarily targets female adolescents and young adults to prevent a disease generally considered a disease of the aged. These issues will significantly influence the willingness of: 1) health policy makers to introduce the vaccine in the health system; 2) health care providers to recommend HPV vaccination; 3) parents to have their children vaccinated; and 4) adolescent and young girls to receive vaccination. Parental awareness and attitude towards the HPV vaccine are likely to be major determinants of acceptability in India.

A survey in Eastern India among educated urban men and women (N = 121), with at least one girl child and belonging to middle or high socio-economic group, revealed that 72% had never heard of HPV. Only 46% of parents were in favor of vaccinating their daughters against an STI; however, after going through a brief information sheet about the HPV vaccine, 80% agreed to vaccination. About 62% of those who accepted the vaccine did not agree that vaccination would be construed as parental consent for children to engage in sexual practice, while 20% were unsure. The most common reason for not accepting the vaccine was uncertainty about the safety of a new vaccine. The physician's recommendation was found to be the most important factor influencing their decision. In the realistic policy scenario, a perceived urgent necessity to introduce HPV vaccines is highly unlikely given the backdrop of practically nonexistent public demand to introduce HPV vaccines and the very low awareness of the viral etiology of cervical cancer and the possibility of preventing it by vaccination. On the other hand, India has a large and rapidly expanding middle-income population. Once the HPV vaccine is licensed in India, it may disseminate through private practice for affluent sections of the society, but it will have little impact on cervical cancer burden unless the socially disadvantaged high-risk populations are covered through public health services.

Difficulties in Organizing Screening Programs in India

Resource constraint has been a major hurdle in organizing screening programs. It has been estimated that in India, even with a major effort to expand cytology services, it will not be possible to screen even one-fourth of the population once in a lifetime in the near future [Directorate General Of Health Services, 1984; Stjernsward et al., 1987). In most developing countries, there has been no success to develop a high quality cytology service. In addition to other resource constraints, deficiencies in record keeping in cytology laboratories and cancer registries make the administrative monitoring and evaluation activities difficult, if not impossible. There is a need to look at alternate practicable options for developing countries.

In the absence of a state policy on cervical cancer prevention, screening of asymptomatic women is practically absent, even among otherwise well-organized health care programs of the industrial and military sectors. Beyond research studies, demonstration projects and provincial efforts in selected districts, there are no serious efforts to introduce population-based screening by public health authorities in almost the entire country. The large burden and suffering from cervical cancer are often underappreciated and there is no effective advocacy for cervical cancer screening and prevention from the general public or professional organizations, such as Federation of Obstetric & Gynaecology Societies of India (FOGSI), as well as the general gynaecology, primary care and cancer control community. Hence, prevention of cervical cancer continues to be largely neglected in India. A major thrust in the National Cancer Control Program has been to detect early stage invasive cancer by early clinical detection/ diagnosis and treatment. At the national policy level, the most cost-effective control option of screening for CIN and preventing invasive cancer is yet to be seriously pursued in India.

Frequency of screening

Efforts should be made to direct resources to women who have not been screened rather than repeated screening. It has also been considered that 'once in a lifetime' screening approach could form an important strategy for a country like India. As discussed earlier, reduction in cumulative incidence rate of cervical cancer in the age group of 35-64 years with different screening intervals worked out to be in the range of 93-64% for

the screening intervals of 1 to 10 years. It has also been worked out in the Indian situation that 'once in a lifetime' screening would result in reduction of 20-30% in the lifetime risk of cervical cancer (IARC, 1986; Murthy et al., 1993; Juneja et al., 1997). This approach could also be one of the options for the limited resource conditions.

Limitations of screening in India

Clifford et al have suggested that cost-effective test could include subset of high-risk HPV, which are more likely to progress to cancer (Clifford et al., 2005). Cervical cancer screening practices are inconsistent in India. Use of Pap smear, as a sole indicator for screening has limitations. The cytological interpretation becomes faulty if the smear is inflammatory; a situation not frequent among women from low socio-economic background. In a scenario of infrequent screening, screening with a test of high sensitivity provides greater reassurance, that potential disease has not been missed in women who screened negative. It is an irony that middle and high socioeconomic women, who can afford HPV screening by molecular techniques, require it the least, owing to low prevalence. Index study has identified illiterate women and those from rural and low-socioeconomic background to be at a greater risk for HPV (Aggarwal et al., 2009). Most of these cases are detected in late stages of disease with poor long-term survival and high rates of death. Strategies involving cytology screening and multiple visits for diagnosis and treatment are impractical in low-resourced and most medium-resourced developing countries (Sanakaranarayan et al., 2005). Several new technologies like fluid-based thin-layer processing of cervical samples to reduce sampling error and automated Pap testing attempts to reduce lab-screening are being explored in an effort to improve the screening accuracy of Pap smears. Though these approaches may be efficient, they add considerable cost to the Pap smear based programs.

Other Factors Influencing Women's Health Care in India

Barriers for women health care

Women encounter many barriers to health care including access to care and gender discrimination (McInlay, 1996). Accessing curative health care in the government health infrastructure in India is difficult because of deficiencies (e.g. non-functioning health centres, non-availability of basic services, private health care, exploitation, medical deceit, etc.), widespread corruption (Sen Amartya, 2005), distance, approach, and especially in the case of women, lack of perception of needs and social support during illness (Priya, 2006). Between 1986 and 1995 the number of people unable to afford health care doubled, i.e., increased from 10 to 21% in urban areas and from 15 to 24% in villages, while at least 40% of hospitalized people borrow or sell assets to pay for their expenses and such out-of pocket expenses may push 2.2% of the population below the poverty line in one year (World Bank India, 2001). An untreated ailment (9-17%) is a common phenomenon in India, more in rural than urban areas with the phenomenon more common among women as they accept such symptoms as part of their normal life (Dilip, 2003). Thus the majority of women at risk for cervical cancer are deeply entrenched in the 'poverty trap' for which they know there is absolutely no recourse (Watkins, 1995) and even 'catastrophe expenditure' is not feasible. Women's socialization into a mindset of self denial and the family's clear prioritization to the needs of its male members does not allow early action on women's illness (Priya, 2006). The main cause for not taking any kind of treatment in general, i.e. economic, along with underreporting of illnesses in women and gender inequality (Watkins, 2005) may contribute to the decreasing trend documented by the registries. Perhaps women who previously had access to health care no longer do this and hence cervical cancer has become less of a concern in India. If so, this has health-policy implications.

Male partner and elders

The male partner and the male elders in the family will need to be made aware about women health care issues through local hospitals and Health Care centres. Rural (66.39%) and urban underprivileged (37.87%) women said that they required the permission and consent of their menfolk to undergo the test (Vallikad et al., 1998). A high level of gynecological morbidity in rural women in India has been documented, where it was observed that 92% of women had at least one disease of the reproductive tract (Bang et al, 1989). Hence the involvement of men is important to facilitate the treatment of both the partners.

Socioeconomic factors and education

Poverty is the real context of India (Duggal and Gangolli, 2005). Two major impediments that are beyond the scope of the strategy are socioeconomic progress and facilities for education. Observations related to socioeconomic status and cervical cancer have already been made. While latrine, bathing and cooking facilities and water supply are basic living requirements, 24.8% and 76.7% of women with cancer of the cervix reported absence of bathing and latrine facilities, respectively. While 11.6% used the kitchen to bathe, 25.6% could bathe only once a week Vallikad et al., 1998). The observations about the educational status of women with cervical cancer and their spouses have already been indicated. An education policy with emphasis on primary education will have a bearing on cervical cancer, the best example being the state of Kerala (Ratcliffe, 1993). A general improvement in socioeconomic status and educational attainment of women contributed to the reduction of incidence and mortality from cervical cancer in developed countries before the introduction of screening programmes (Laara et al., 1987). Thus screening for cervical cancer represents a microcosm of social development (Paskett, 2004). Developing and implementing any kind of preventive health intervention for the impoverished and excluded is a formidable task, as they are most often beyond the realm of curative medicine. However challenging the task may be, these efforts still must be made.

Gaps that need to be filled

Colposcopy and treatment facilities for precancerous lesions are not available in most areas of India and doctors and gynaecologists are mostly not used to providing routine cervical screening or other preventive health care services. There are large gaps in provider knowledge and practices, due to limited training and reorientation opportunities. For screen-positive women and those with precancerous lesions, availability and access are limited to appropriate diagnostic (e.g., colposcopy) and treatment (e.g., cryotherapy, loop electrosurgical procedure (LEEP), laser, etc.) services. Most women with CIN are often inappropriately managed by hysterectomy in many urban and rural areas. Facilities for management of invasive cervical cancer by radiotherapy and chemotherapy are more widely developed compared to colposcopy and management of precancerous lesions. Policy makers, social advocates and the general population are largely unaware of the potential for early detection of cervical precancerous lesions and the prevention of cervical cancer. Although task forces have deliberated the problem of cervical cancer and have made recommendations, organized mass screening is not yet a reality in India.

Conclusion

India has become a destination of choice for multinational studies in the field of oncology due to the large patient numbers, improving regulatory processes that are being implemented, investigators who are research and academically inclined and the large number of patients. There is no doubt that the control of cancer of the uterine cervix is an important issue for the health planners. Screening practices can preferentially be directed to the target population for optimal utilization of resources. Needless to say, health education, promotion of condom usage and need to follow healthy hygienic practices is the most cost-effective approach in reducing the incidence of cervical carcinoma in resource-crunched societies like India. Cervical cancer control activities could be included in the existing 'reproductive and child health program.' With expansion in absolute number of cases of cancer set to continue, the role of prevention in cancer control strategies would therefore remain central.

Acknowledgements

The authors are grateful to Dr. Paul Dinakaran, (the Chancellor), Dr. Paul P. Appasamy, (the Vice Chancellor) and Dr. Anne Mary Fernandez, (the Registrar), of Karunya University, Coimbatore, India, for their constant support and encouragement. The authors declare that they have no conflict of interest.

References

Aggarwal R, Gupta S, Nijhawan R, et al (2009). Prevalence of high-risk human papillomavirus infections in women with benign cervical cytology: A hospital based study from North India. Indian J of Cancer, 43, 110-116

Alliance for Cervical Cancer Prevention (ACCP) (2004). Planning and Implementing Cervical Cancer Prevention and Control Programs: A Manual for Managers. Seattle: ACCP.

Arbyn M, Sasieni P, Meijer CJ, et al (2006). Chapter 9: Clinical applications of HPV testing: A summary of meta-analyses. Vaccine, 24, 78-89.

Bang RA, Bang AT, Baitule M, et al (1989). High Prevalence of Gynaecological diseases in Rural Indian Women. Lancet, 1, 85-88

Basu PS, Sankaranarayanan R, Mandal R, et al (2003). Visual inspection with acetic acid and cytology in the early detection of cervical neoplasia in Kolkata, India. Int J Gynecol Cancer, 13, 626–32.

Belinson JL, Pretorius RG, Zhang WH, Wu LY, Qiao YL, et al (2001). Cervical cancer screening by simple visual inspection after acetic acid. Obstet Gynecol 98, 441–44.

Bhatla N, Dar L, Patro AR, Kriplani A, Gulati A, et al (2006). Human papillomavirus type distribution in cervical cancer in Delhi, India. Int J Gynecol Pathol 25, 398-402.

Cancer Atlas India. Available at: http://www.canceratlasindia.org/chapter6.asp (last accessed: April 2008).

Cervical cancer: Fact sheet. National Institute of Health, September 2007.

Clifford GM, Gallus S, Herrero R, et al (2005). Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. Lancet, 366, 991–8.

Clifford GM, Smith JS, Plummer M, Munoz N, Franceschi S (2003). Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. Br J Cancer, 88, 63–73.

Curado MP, Edwards B, Shin HR, et al (2007). Cancer Incidence in Five continents. IARC Scientific Publications No 160, Lyon: IARC Press, Lyon pp 90.

Dabash R, Vajpayee J, Jacob M, et al (2005). A strategic assessment of cervical cancer prevention and treatment services in 3 districts of Uttar Pradesh, India. Reprod Health 2, 11.

Denny L, Kuhn L, De Souza M, et al (2005). Screen and-treat approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial. JAMA, 294, 2173-81.

Denny L, Kuhn L, Pollack A, Wainwright H, Wright T (2000). Evaluation of alternative methods of cervical cancer screening in resource poor settings. Cancer, 89, 823-26.

Denny L, Kuhn L, Pollack A, Wright TC Jr (2002). Direct visual inspection for cervical cancer screening: an analysis of factors influencing test performance. Cancer, 94, 1699–707.

Dilip TR (2005). Extent of Inequity in Access to Health Care Services in India. In 'Review of Health Care in India', Eds Gangolli LV, Duggal R, Shukla A. Review of Health Care in India. Centre for Enquiry into Health and Allied Themes, pp. 247-268.

Directorate General of Health Services (1984). National Cancer Control Program of India. Government of India, New Delhi.

Duggal R, Gangolli LV (2005). Introduction to Review of Healthcare in India. In 'A Review of Healthcare in India', Eds Gangolli LV, Duggal R, Shukla. A Review of Healthcare in India. Centre for Enquiry into Health and Allied Themes, pp. 3-18.

Ferenczy A, France E (2002). Persistent human papillomavirus infection and cervical neoplasia. Lancet Oncology, 3, 11-16.

Ferlay J, Bray F, Pisani P and Parkin DM (2001). GLOBOCAN 2000: cancer incidence, mortality and prevalence worldwide. Version 1. 0. Lyon: IARC Press.

Ferlay J, Bray F, Pisani P, Parkin DM (2004). GLOBOCAN 2002. Cancer Incidence, Mortality and Prevalence Worldwide. IARC Cancer Base No. 5 Version 2.0. Lyon: IARC Press.

Franceschi S, Rajkumar R, Snijders PJ, et al (2005).

Papillomavirus infection in rural women in southern India. Br J Cancer, 92, 601–6.
Franceschi S, Rajkumar T, Vaccarella S, et al (2003). Human papillomavirus and risk factors for cervical cancer in Chennai, India: a case-control study. Int J Cancer, 107, 127–33.
Gajalakshmi V, Rajaraman S, Shanta V (2000). A survival study of cancer in Chennai, India. Indian J. Cancer; 37, 158-164.
Gheit T, Vaccarella S, Schmitt M, et al.(2009). Prevalence of human papillomavirus types in cervical and oral cancers in central India. Vaccine 27, 636-639.
Goldie S, Galkin L, Goldhaber-Fiebert J, et al (2005). Cost effectiveness of cervical screening in five developing countries. N Eng J Med, 353, 2158–2168.
Goldie SJ, Kuhn L, Denny L, Pollack A, Wright TC (2001). Policy analysis of cervical cancer screening strategies in low-resource settings: clinical benefits and cost-effectiveness. JAMA, 285, 3107–15.
IARC Handbooks on Cancer Prevention (2004). Cervix cancer screening. IARC Press, Lyon, 10.
IARC Working Group (1995). Human Papillomaviruses. IARC Monograph on the Evaluation of Carcinogenic Risks to Humans. Lyon: International Agency for Research on Cancer, 65.
IARC working group: Summary (1986). In 'Screening for cancer of uterine cervix', Eds Hakama M. IARC scientific Publication No 76, Lyon, pp 133-42.
International Institute for Population Sciences (IIPS). National Family Health Survey (NFHS-3), India. 2005–2006. Ministry of Health and Family Welfare, Government of India. Available at: http://www.nfhsindia.org/pdf/IN.pdf (last accessed: April 2008).
Kim JJ, Ortendahl J, Goldie SJ (2009). Cost-Effectiveness of Human Papillomavirus Vaccination and Cervical Cancer Screening in Women Older Than 30 Years in the United States. Annals of Internal Medicine 151, 538-545.
Juneja A, Murthy NS, Tuteja RK, Sardana S, Das DK (1997). Reduction in the cumulative incidence rate of cervical cancer by one life time selective screening. Neoplasma 44, 272-4.
Sarkar K, Bhattacharya S, Bhattacharyya S, Chatterjee S, Mallick AH, Chakraborti S, et al. (2008). Oncogenic human papilloma virus and cervical pre- cancerous lesions in brothel-based sex workers in India. Journal of Infection and Public Health 1, 121-128.
Krishnan Nair M, Sankaranarayanan R (1991). Epidemiological lead to cancer control. Cancer causes Control 2, 263-265.
Laara E, Day NE, Hakama M (1987). trends in mortality from cervical cancer in the Nordic countries: association with organized screening programmes. Lancet I, 1247–1249
Laikangbam P, Sengupta S, Bhattacharya P, et al (2007). A comparative profile of the prevalence and age distribution of human papillomavirus type 16/18 infections among three states of India with focus on northeast India. Int J Gynecol Cancer 17,107–17.
Legood R, Gray AM, Mahe C, et al (2005). Screening for cervical cancer in India: How much will it cost? A trial based analysis of the cost per case detected. Int J Cancer, 117, 981–7.
Londhe M, George SS, Seshadri L (1997). Detection of CIN by naked eye visualization after application of acetic acid. Indian J Cancer 34, 88–91.
Mandal R, Mittal S, Basu P (2003). Management of cervical precancer. In 'Detection, diagnosis and management of cervical intraepithelial neoplasia'. Eds Lodha ND, Kamal MM. Nagpur, 1.
Mandelblatt JS, Lawrence WF, Galkin L, et al (2002). Costs and benefits of different strategies to screen for cervical cancer in less-developed countries. J Natl Cancer Inst, 94, 1469–83.
McInlay JB (1996). Some contributions from the social system to gender inequalities in heart disease. J Health Soc Behav, 37, 1-26.
Munirajan AK, Kannan K, Bhuvarahamurthy V, Ishida I, Fujinaga K, Tsuchida N, et al (1998). The status of human papillomavirus and tumor suppressor genes p53 and p16 in carcinomas of uterine cervix from India. Gynecol Oncol, 69, 205–9.
Murthy NS, Agarwal SS, Prabhakar AK, Sharma S, Das DK (1993). Estimation of reduction of life-time risk of cervical cancer through one life-time screening. Neoplasma, 40, 255-8.
National Sample Survey, 42nd and 52nd Round. National Sample Survey Organisation, Government of India. New Delhi.
Nene BM, Jayant K, Arrossi S, Shastri S, Budukh A, Hingmire S, et al (2007). Determinants of womens participation in cervical cancer screening trial, Maharashtra, India. Bull World Health Organ, 85, 264–72.
Parashari A, Singh V, Sehgal A, Satyanarayana L, Sodhani P, Gupta MM (2000). Lowcost technology for screening uterine cervical cancer. Bull World Health Organ, 78, 964-7.
Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB (2002). Cancer incidence in five continents. IARC Scientific Publication, 8, 155.
Paskett ED, Wewers ME, Ruffin MT (2004). Educational Strategies for the Prevention of Cervical Cancer. In 'Cervical Cancer: From Etiology to Prevention', Eds Rohan TE, Shah KV. Kluwer Academic Publishers USA. 9, pp237-259.
Peedicayil A, Abraham P, Sathish N, John S, Shah K, Sridharan G, et al (2006). Human papillomavirus genotypes associated with cervical neoplasia in India. Int J Gynecol Cancer, 16, 1591–5.
Priya R (2006). Towards 'Health Security' for Women and Children: Exploring Debates and Options. In 'Securing Health for All Dimensions and Challenges', Eds Prasad S, Sathyamala C. Institute for Human Development, New Delhi pp.328-352.
Priyanka Golikeri (2009). A new vaccine for cervical cancer and some good hope. Available at: http://cancersupport.aarogya.com/index.php?option=com_content&task=view&id=333&Itemid=361. Accessed November 2009
Qiao YL, Sellors JW, Eder PS, et al (2008). A new HPV-DNA test for cervical-cancer screening in developing regions: a cross sectional study of clinical accuracy in rural China. Lancet Oncol, 9, 929-36.
Rao DN, Ganesh B (1998). Estimate of cancer incidence in India in 1991. Indian J Cancer, 35, 10-8.
Ratcliffe J (1983). Social justice and the demographic transition: lessons from India's Kerala State In 'Practicing Health for All', Eds Morley D, Rohde J and Williams G. Oxford University Press, pp 64-82.
Sangwa-Lugoma G, Mahmud S, Nasr SH, et al (2006). Visual inspection as a cervical cancer screening method in a primary health care setting in Africa. Int J Cancer , 119, 1389–95.
Sankaranarayanan R, Basu P, Wesley RS, Mahe C, Keita N, Mbalawa CC, et al (2004). Accuracy of visual screening for cervical neoplasia: Results from an IARC multicentre study in India and Africa. Int J Cancer, 110, 907–13.
Sankaranarayanan R, Budukh A and Rajkumar R (2001). Effective screening programs for cervical cancer in low- and middle-income developing countries. Bull World Health Organ, 79, 954–962.
Sankaranarayanan R, Chatterji R, Shastri SS, Wesley RS, Basu P, Mahe C, et al (2004). Accuracy of human papillomavirus testing in primary screening of cervical neoplasia: results from a multicenter study in India. Int J Cancer, 112, 341–7.
Sankaranarayanan R, Esmi A, Jayaraman R, Cherian J, Parkin

DM (2000). Leads to cancer control based on cancer patterns in a rural population in south India. Cancer Causes Contr, 11, 433–9.

Sankaranarayanan R, Esmy PO, Rajkumar R, Muwonge R, Swaminathan R, Shanthakumari S, et al (2007). Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. Lancet, 370, 398–406.

Sankaranarayanan R, Gaffikin L, Jacob M, Sellors J, Robles S (2005). A critical assessment of screening methods for cervical neoplasia. Int J Gynaecol Obstet, 89(2):4–12.

Sankaranarayanan R, Nene BM, Dinshaw KA, Mahe C, Jayant K, Shastri SS, et al (2005). A cluster randomized controlled trial of visual, cytology and human papillomavirus screening for cancer of the cervix in rural India. Int J Cancer, 116, 617–23.

Sankaranarayanan R, Rajkumar R, Arrossi S, Theresa R, Esmy PO, Mahe C, et al, (2003). Determinants of participation of women in a cervical cancer visual screening trial in rural south India. Cancer Detect Prev,27, 457–65.

Sankaranarayanan R, Rajkumar R, Esmy PO, Fayette JM, Shanthakumary S, Frappart L, et al (2007). Effectiveness, safety and acceptability of 'see and treat' with cryotherapy by nurses in a cervical screening study in India. Br J Cancer, 96, 738–43.

Sankaranarayanan R, Rajkumar R, Theresa R, et al (2004). Initial results from a randomized trial of cervical visual screening in rural south India. Int J Cancer, 109, 461–67.

Sankaranarayanan R, Shastri SS, Basu P, Mahe C, Mandal R, Amin G, et al (2004). The role of low-level magnification in visual inspection with acetic acid for the early detection of cervical neoplasia. Cancer Detect Prev, 28, 345–51.

Sankaranarayanan R, Thara S, Sharma A, Roy C, Shastri S, Mahe C, et al (2004) . Accuracy of conventional cytology: results from a multicentre screening study in India. J Med Screen, 11, 77–84.

Sankaranarayanan R, Wesley R, Thara S, et al (2003). Test characteristics of visual inspection with acetic acid (VIA) and Lugol's iodine (VILI) in cervical cancer screening. Int J Cancer, 106, 404–8.

Sankaranarayanan R, Wesley R. A Practical manual on visual screening for cervical neoplasia (2003). IARC Technical Publication No. 41, Lyon: IARC Press.

Schensul SL, Mekki-Berrada A, Nastasi BK, Singh R, Burleson JA, Bojko M (2006). Men's extramarital sex, marital relationships and sexual risk in urban poor communities in India. J Urban Health, 83, 614–24.

Sellors J, Sankaranarayanan R (2003). Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: IARC Press.

Sen Amartya (2005). Introduction. In 'The Delivery of Primary Health Services. A Study in West Bengal and Jharkhand.' The Pratichi Health Report Number 1. TLM Books with Pratichi (India) Trust.

Shanta V, (2003). Perspectives in Cervical Cancer prevention in India. The International Network for Cancer Treatment and Research.

Shastri SS, Dinshaw K, Amin G, Goswami S, Patil S, Chinoy R, et al (2005). Concurrent evaluation of visual, cytological and HPV testing as screening methods for the early detection of cervical neoplasia in Mumbai, India. Bull World Health Organ, 83, 186–94.

Sowjanya AP, Jain M, Poli UR, Padma S, Das M, Shah KV, et al (2005). Prevalence and distribution of high-risk human papilloma virus (HPV) types in invasive squamous cell carcinoma of the cervix and in normal women in Andhra Pradesh, India. BMC Infect Dis, 5, 116.

Stjernsward J, Eddy D, Luthra UK and Stanley K (1987). Plotting a new course for cervical cancer in developing countries. World Hlth Frm, 8, 42-45

University of Zimbabwe/JHPIEGO Cervical Cancer Project (1999): visual inspection with acetic acid for cervical cancer screening: test qualities in a primary-care setting. Lancet, 353, 869–73.

Vallikad E, Krishnan S, Kumaraswamy (1998). Studies, Strategies and Concepts for Women's Health in Women's Hands: A Community Approach for the Control of Cancer Cervix in Karnataka, India. Kidwai Mem. Instit. Onco. Bangalore, India.

Walboomers JMM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah IV, et al (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. Journal of Pathology, 189, 12-19.

Watkins K (1995). The Oxfam Poverty Report. Oxford, UK. The Pratichi Research Team. The Delivery of Primary Health Services. A Study in West Bengal and Jharkhand. The Pratichi Health Report. Number 1. 2005, TLM Books with Pratichi (India) Trust.

World Bank India (2001): Raising the Sights – Better Health Systems for India's Poor. Report No. 22304.

World Health Organisation (1986). Control of Cancer Cervix. Bull. WHO, 64,607-618.

World Health Organization Vaccine Preventable Diseases Monitoring System. Available at: http://www.who.int/vaccines/globalsummary/immunization/countryprofileselect.cfm (last accessed: April 2008)

World Health Organization (2006). Comprehensive cervical cancer control. A guide to essential practice. Geneva: WHO.

World Health Organization. Reproductive health indicators database. Available at: http://www.who.int/reproductive-health/global monitoring/RHRxmls/RHRmainpage.htm (last accessed: April 2008).