

## Present Status of Cervical Neoplasia Control and Human Papilloma Virus Epidemiology in India: The Wind is Blowing; Unfolding the Truth

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### Abstract

By reviewing of previous studies, concentrating on recent systematic reviews and large prospective studies tries to give a clear picture with epidemiological evidence about the present scenario of cervical cancer control and HPV (Human Papilloma Virus) in India. Cervical cancer is the second most common cancer among women worldwide and most common malignancy in developing countries, particularly in India. It is unique among cancers in that it can largely be prevented through screening and removal of pre-cursor lesions. Nowadays, cervical screening for women is necessary because there are no signs and symptoms of cervical pre-cancers. 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 most of the population once in a lifetime in the near future. New HPV vaccines will also help prevent HPV infection and the pre-cancerous changes that lead to cervical cancer. The focus on identification and prevention of cervical cancer must be emphasized in a highly populated country like India to prevent its extensive blowout.

**Keywords:** Cervical neoplasia; Screening; Human papilloma virus; Vaccine; India

### Background

Cancer is the most progressive and devastating disease showing a threat of mortality to the entire world despite significant advances in medical science for its diagnosis and treatment. It is estimated that by the year 2020 there will be almost 20 million new cases. Worryingly, the proportion of new cases from the developing countries like India will rise to around 70%. The scale of the problem of cancer in the Indian Sub-Continent is alarming [1]. 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 [2]. 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. The risk of cervical cancer remains high in many developing countries mostly due to the lack or inefficiency of existing prevention programmes. This review tries to give a brief picture about the scenario of cervical cancer prevention and HPV epidemiology in India.

### Outlines of Prevalence of Cervical Neoplasia in India

Significant amounts of cervical cancer patients shown in the Indian sub-continent. There is an estimated annual global incidence of 500000 cancers, in that India contributes 100000 i.e., one-fifth of the world burden [3]. Recently a report says that there are an estimated 1.32 lakh new cases and 74000 deaths annually in India [4]. The number of cervical cancer deaths in women in India is projected to increase to 79000 by the year 2010. 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. The peak incidence was observed in older women 70 years of age [5]. 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. There is considerable awareness, advocacy and investment to reduce maternal deaths among policy makers, governments, professional societies

[including the Federation of Obstetrics and Gynaecology Societies of India (FOGSI), 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.

### Risk factors for Cervical Neoplasia

Epidemiological studies have identified a number of risk factors such as infection with certain oncogenic types of Human Papilloma Viruses (HPV), sexual intercourse at an early age, multiple sexual partners, long-term oral contraceptive use, multi-parity, low socio-economic status, tobacco smoking, infection with *C. trachomatis*, micronutrient and diet deficiency that contribute to the development of cervical cancer [6]. 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 cancer [7].

### HPV Epidemiology in 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 high risk 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 HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 [8]. Overall HPV prevalence in India was similar to the high-risk areas in Latin America [9]. The prevalence of any HPV type was 16.9%

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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 [10]. In a multi-center, 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 [11]. Unlike most populations in developed countries, HPV prevalence was constant across age groups in India, with no clear peak in young women. Low clearance of incident infections, frequent re-infection/reactivation, under representation of teenagers in the study samples and sexual behavioral patterns in the population may be responsible for the constant, stable 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 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. 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 [12]. 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 [13]. Eighteen HPV types were identified in cervical cancer specimens in a study in Vellore [14]. Ideally, a 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.

## Screening of Cervical Neoplasia

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. 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. 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. 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. The difficulties in implementing an organized cervical cytology screening in India 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. 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 [15].

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.

## Papanicolaou smears

Papanicolaou (Pap) smears are used to screen for cervical cancer. 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.

## Visual Inspection with Acetic acid (VIA)

Cervical neoplasia 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 involves visually examining the cervix for lesions with the naked eye no magnification after the application of a 3-5% acetic acid wash to visualize definite, opaque aceto-white lesions close to the squamocolumnar junction [16]. In several studies, VIA had an acceptable sensitivity in detecting Cervical Intraepithelial Neoplasia (CIN). 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% [17].

## HPV testing

HPV testing is done for the detection of specific high risk HPV types. In 2000, Sankaranarayanan et al., [2] done HPV testing in a cluster-randomized controlled trial on HPV screening for cervical cancer in rural India; Osmanabad; Maharashtra and 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. However, since most HPV infections in young women regress rapidly without causing clinically significant disease, such an approach raises a legitimate concern. A drawback to HPV testing is that it is more expensive, test costs around Rs.1350 per test in private medical centers in India.

## HPV vaccination

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 HPV-18 and are given in three doses over a six-month period. 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. 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. 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 taking the vaccine was uncertainty about the safety of a new vaccine. In the realistic policy scenario, a perceived urgent necessity to introduce HPV vaccines is highly unlikely given the backdrop of practically non-existent 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 distribute 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.

### **Problem Encountered During Screening; Unseen Concern and Challenges**

1. 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. 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.

2. In the absence of a state policy on cervical cancer prevention, screening of asymptomatic women is practically absent. 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 Obstetrics and 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. 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.

### **Measures to Counteract the Problems**

1. 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. 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 life-time risk of cervical cancer [18]. This approach could also be one of the options for the limited resource conditions.

2. 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 [19].
3. Women in India encounter many barriers to health care including access to care and gender discrimination [20]. Accessing curative health care in the government health infrastructure in India is difficult because of deficiencies (e.g. non-availability of basic services, private health care, exploitation, medical deceit, etc.), distance, approach, and especially in the case of women, lack of perception of needs and social support during illness [21]. 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 [22]. The main cause for not taking any kind of treatment in general, i.e. economic, along with under reporting of illnesses in women and gender inequality 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.
4. 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 centers. Rural women said that they required the permission and consent of their male partner to undergo the test [23]. A high level of gynecological morbidity in rural women in India has been documented.
5. Low economic status is the real context of India. Two major impediments that are beyond the scope of the strategy are socioeconomic progress and facilities for education. Observations related to socio economic status and cervical cancer have already been made. The observations about the educational status of women with cervical cancer and their spouses have already been indicated. 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. Thus screening for cervical cancer represents a microcosm of social development [24]. 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.

### **The Way Onward**

Colposcopy and treatment facilities for precancerous lesions are not available in most areas of India and doctors 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., loop electrosurgical procedure, laser, etc.) services.

## Conclusion

India has become a hotspot for multicenter 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. Health education, safe sex and need to follow healthy hygienic practices are the most cost-effective approach in reducing the incidence of cervical carcinoma in resource-crunched societies like India.

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