Prevention of Cervix Cancer in India

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Key Words

Cervical cancer · Prevention · Screening · HPV vaccine

Abstract

Cervical cancer is the fourth most common cancer among women globally and the second most common cancer among Indian women. India alone bears 23% of the global cervical cancer burden. In India, population-based cervical cancer screening is largely nonexistent in most regions due to competing healthcare priorities, insufficient financial resources and a limited number of trained providers. Hence, most of the cases present in advanced stages of the disease, thus leading to increased mortality and reduced survival. Various screening options like cytology, visual-based screening and testing for high-risk HPV are available. Several cross-sectional studies have looked at the comparative efficacy of different screening tests. Three important randomized controlled trials from India have shown the efficacy of screening once in a life time with HPV DNA, one-time screening with VIA by trained nurses and four-time screening with VIA by trained primary health workers, reducing mortality due to cervical cancers. Prevention of cervical cancers with two-dose HPV vaccination and early detection of precancerous cervical lesions of the eligible population through screening and their appropriate treatment with a single-visit 'screen-and-treat' approach appear to be promising for low-middle-income countries including India.

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Introduction

Globally, cervical cancer is the fourth most common cancer in women, with an estimated 560,505 new cases and 284,923 deaths in 2015. The vast majority, around 85% of cervical cancer cases and 87% of cervical cancer deaths occur in the less developed regions. In these regions, cervical cancer accounts for almost 12% of all female cancers and 10% of all female cancer deaths [1] because of poor access to screening and treatment services [2]. It is the second most common cancer and third most common cause of cancer deaths among women in the less developed regions. In India, cervical cancer is the second most common cancer, with an estimated 132,314 new cases and 73,337 deaths in the year 2015 [1].

Human Papilloma Virus

Infection with high-risk human papilloma virus (HPV) and its persistence are necessary though not sufficient causes of cervical cancer. HPV is the most common viral infection of the reproductive tract. It is generally acquired by young women after the onset of sexual activity. The majority of HPV infections do not cause symptoms or disease and resolve spontaneously within 2 years. According to a meta-analysis of one million women with normal cytological findings, the adjusted HPV prevalence worldwide was estimated to be 11.7% [3]. Per-

sistent infection with high-risk HPV genotypes may result in cervical pre-cancer which, if untreated, may progress to cervical cancer. The challenge is to identify the etiologic cofactors responsible for the persistence of HPV infection and its progression to neoplastic changes. There are more than 150 types of HPV. Amongst these, the International Agency for Research on Cancer (IARC) has defined 12 high-risk HPV types that are associated with cancers in humans (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) [4]. Worldwide, the most frequent HPV types are 16 and 18, with HPV 16 being the most common subtype [3]. Globally, 70% of invasive cervical cancers are caused by infection with HPV 16 and 18. 41–67% of high-grade squamous intraepithelial lesions, 16–32% of low-grade squamous intraepithelial lesions and 6–27% of atypical squamous cells of undetermined significance are also estimated to be HPV 16/18 positive [5]. It takes 10 years or longer from the time HPV infection is acquired to its progress to invasive carcinoma. Cervical lesions can occur by coinfection or subsequent infection with several HPV types [6]. There is no concrete evidence regarding whether natural infection with HPV induces protection against reinfection. However, there appears to be a reduced risk of reinfection with the same HPV type. The infection does not seem to provide group-specific or general immune protection from reinfection with other HPV types [7]. The prevalence of persistent HPV infection, infection with multiple HPV types and the risk of progression to high-grade cervical intraepithelial neoplasia (CIN) and cervical cancer is higher among HIV-infected women as compared to women without HIV infection [8].

Other Risk Factors for Cervical Cancer

Several factors increase the risk of cervical cancer. Early age at onset of sexual activity and multiple sexual partners have been identified as risk factors [9]. IARC has listed tobacco smoking as a risk factor for cervical cancer [10]. A pooled analysis from 23 epidemiological studies showed a 1.5-times greater risk of cervical squamous cell carcinoma among current smokers, with the risk being directly related to the number of cigarettes smoked per day [11]. In the UK, an estimated 7% of cervical cancers are linked to tobacco smoking [12]. High parity, smoking, nutrition and use of combined hormonal oral contraceptives for more than 5 years have been reported as major environmental risk factors for cervical cancer in various studies [13, 14]. Infection with other sexually transmitted diseases such as HIV, herpes, chlamydia, gonorrhea and

syphilis increases the cervical cancer risk. The risk may also be increased in women taking immunosuppressive medications, women on a diet low in fruits and vegetables, women with long-term use of oral contraceptives and women in poverty [9, 13, 14].

HPV Vaccine

Two prophylactic vaccines, a quadrivalent vaccine which protects against HPV 6, 11, 16 and 18 and a bivalent vaccine which protects against HPV 16 and 18, are currently available and marketed in many countries worldwide for the prevention of HPV-related diseases. The quadrivalent vaccine Gardasil (Merck, USA) was licensed in 2006 and the bivalent vaccine Cervarix (Glaxo Smith Klein, Belgium) was licensed in 2007 [7].

HPV vaccines are most efficacious if administered before the onset of sexual activity, i.e. before first exposure to HPV infection. Both vaccines are to be administered as a 0.5-ml intramuscular injection in the deltoid region from the age of 9 years onwards. Two-dose vaccination (0 and 6 months) in girls aged 9–14 years appeared comparable to the standard 3-dose schedule in women aged 15–25 years [15]. The quadrivalent HPV vaccine can be administered according to a 2-dose schedule (0.5 ml at 0 and 6 months) for girls and boys aged 9–13 years. The third dose is essential if the second vaccine dose is administered earlier than 6 months after the first dose. Alternatively, the vaccine can be administered according to a 3-dose schedule for those younger than 14 years (0.5 ml at 0, 2 and 6 months) and needs to be necessarily administered as a 3-dose schedule for those older than 14 years of age, wherein the minimum interval between dose 1 and 2 should be 1 month and the minimum interval between dose 2 and 3 should be 3 months. The bivalent HPV vaccine is recommended as a 2-dose schedule (0.5 ml at 0 and 6 months) for girls aged 9–14 years and as a 3-dose schedule for girls older than 15 years (0.5 ml at 0, 1 and 6 months). If at any age the second vaccine dose is administered before the fifth month after the first dose, the third dose needs to be administered [7]. Both vaccines are to be maintained at 2–8°C and not to be frozen. High antibody titers have been observed for at least 8.4 years for the bivalent vaccine with 100% seropositivity, and for at least 8 years for the quadrivalent vaccine [16, 17]. High efficacy against HPV 16 and 18 infection and CIN 3 lesions was reported in two phase III pre-licensure trials among HPV-naïve vaccine recipients with the quadrivalent vaccine [16, 18]. High efficacy with bivalent vaccine against

infection and cervical lesions associated with HPV 16 and 18 was also observed in two phase III studies [17]. Both vaccines are safe and are associated with mainly short-duration local injection site reactions, particularly pain [19].

The vaccines have not been licensed as 2-dose schedule in all countries and the need for a booster dose has not yet been established. There is no need to screen for HPV infection or HIV infection prior to HPV vaccination. Both HPV vaccines can be coadministered with other non-live and live vaccines using separate syringes and different injection sites [7].

According to the WHO, both the quadrivalent and bivalent HPV vaccines have excellent safety and efficacy profiles. Since the currently available vaccines do not protect against all high-risk HPV types, HPV vaccination remains a primary prevention tool and does not eliminate the need for screening later in life. The WHO recommends the HPV vaccination to be included in the national immunization program in countries where the prevention of cervical cancer and/or other HPV-related diseases constitutes a public health priority and vaccine introduction is programmatically feasible, sustainable and where financing can be secured. Fifty-eight countries (30%) have introduced HPV vaccine in their national immunization program for girls and in some countries also for boys by August 2014 [7]. Vaccination of girls aged 9–12 years in low resource settings with 2-dose HPV vaccine has been recommended [20]. A new vaccine nonavalent (9-valent) to protect against infection from HPV types 16, 18, 6, 11, 31, 33, 45, 52 and 58 is currently under regulatory assessment [21].

Screening and Early Detection of Cervical Cancer

Imparting cancer education (fig. 1) for avoiding risk factors and recognizing possible warning signs, HPV vaccination and early detection of cervical cancer through screening of asymptomatic women, with the aim of detecting and treating precancerous lesions of the cervix, are important measures of cervical cancer control. Several screening options like cytology (conventional, liquid based, automated pap), testing for high-risk HPV and visual-based screening methods have been investigated and practiced in different regions worldwide.

Cytology-Based Screening

The western world adopted high-quality cytology-based cervical cancer screening along with good coverage

Fig. 1. Cancer education sessions.

of the population at risk and was successful in reducing the disease burden. A decline in the incidence rates of invasive cervical cancer by 54% was noted over 35 years in the United States from 1973 to 2007 [22]. In the UK, from 1990 to 2008, women aged 35–64 years participating in a cervical cancer screening program had a reduced risk of cervical cancer of 60–80% and a reduced risk of developing an advanced cervical cancer of 90% over the next 5-year period [23]. An assessment of the impact of a Norwegian coordinated cervical cancer screening program introduced in 1995 in women aged 25–69 years with conventional Pap smear every 3 years, showed a 22% reduction in the incidence of invasive cervical cancer in 6 years following the screening introduction as compared to the 3-year period prior to the screening program [24]. Thus, there is convincing evidence about the benefits of conventional cytology-based screening from several countries of the more developed regions that introduced Pap test in their national cervical cancer screening program. The sensitivity of conventional Pap cytology ranges between 30 and 87%, and its specificity ranges from 86 to 100% in various studies [25].

Some new technologies like the liquid-based cytology (LBC) and the automated Pap smears are also available. LBC is more expensive than conventional cytology. However, it has certain logistical and operational advantages such as interpretation at a higher speed, a lower rate of unsatisfactory smears and the possibility of ancillary molecular testing using remnant fluid. In the UK, since 2008, the screening strategy adopted in the national cervical cancer screening program has been changed from the Pap test to LBC [26]. A meta-analysis comparing conventional Pap with LBC found no difference in the relative sensi-

tivity and specificity when high-grade and low-grade squamous intraepithelial lesions were considered as cut-off [27]. In automated Pap, various characteristics of the cells are noted, and slides that exceed a certain threshold for the likelihood of abnormal cells are most likely the ones selected for manual rescreening [28].

Screening with HPV Test

HPV DNA testing is the most reproducible of all cervical cancer screening tests. Several methods of HPV testing are available. The most commonly used in clinical practice is Hybrid Capture II, which is a batch test based on hybridization. It tests the cervical samples for the presence of 13 high-risk HPV types above a certain threshold (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). It necessitates the presence of sophisticated laboratory infrastructure and trained technicians. The PCR-based assay utilizes target amplification with the advantage of identifying different HPV types and thus helps in discriminating between multiple infections. Its major disadvantages are that it is expensive, time-consuming and laborious; hence, it is used more in research settings [29]. HPV as a screening test has a very good sensitivity and a high negative predictive value, thus allowing lengthening of the screening intervals. A meta-analysis showed a pooled sensitivity of HC2 for detecting CIN 2 and above lesions of 89.3% with the pooled specificity of 87.8% [30]. A randomized controlled trial (RCT) was conducted in the Osmanabad district in India to test the efficacy of a single round of cervical cancer screening by HPV, cytological testing or visual inspection of the cervix with acetic acid (VIA) on the incidence and mortality of cervical cancer. The trial reported a significant 48% reduction in mortality from cervical cancers after 7 years following a single round of HPV testing [31].

careHPV is a simple rapid portable test that has recently been launched for detecting 14 high-risk HPV types. With this, the patient can be managed with a single-visit approach [32]. The persistence of oncogenic HPV indicated by the upregulated expression of HPV E6/E7 genes is necessary for the initiation and progression of cervical neoplasia [33]. Hence, it is being investigated as a biomarker for cervical cancer screening in different circumstances. This test has the potential to be reliable for both primary cervical cancer screening and for triage purposes. The HPV DNA test has high sensitivity but low specificity for the detection of CIN 2 and above lesions. A prospective study evaluating the efficacy of mRNA testing for predicting high-grade lesions in women positive for HPV 16 and/or 18 DNA showed its usefulness as a

triage test [34]. A retrospective study evaluated the performance of E6/E7 mRNA assay as a triage test for cytology and HPV DNA testing. It demonstrated that mRNA was a better triage test than HPV DNA for cytology-positive cases and was also more efficient than cytology for the triage of HPV DNA-positive women. However, because of its low sensitivity, strict follow-up of HPV DNA positive and mRNA negative cases is advised [35]. Sampling of the vaginal fluid for high-risk HPV detection by HPV self-sampling has been tried in various regions using different devices, especially in conditions where universal cytology programs are not available or subgroups of women that are difficult to reach via traditional screening programs. In general, the studies show good acceptance and fairly good diagnostic accuracy. This may act as a valuable method among women who refuse to attend clinic-based screening [36].

Screening with Visual-Based Techniques

Cytology- or HPV-based cervical cancer screening is currently not a feasible option for population-based screening in low-income countries including India due to lack of resources, trained staff and infrastructure. Hence, alternative low-cost and effective cervical cancer screening methods that can be performed by medical as well as paramedical staff have been explored. Several methods like visual inspection of the cervix with the naked eye after application of acetic acid (VIA) (fig. 2), after magnification (VIAM) and after application of Lugol's Iodine (VILI) (fig. 3) have been investigated. These tests have good sensitivity but lack good specificity. The sensitivity and specificity in a pooled analysis of 11 cross-sectional studies across India and Africa were 76.8 and 85.5% for VIA and 91.7 and 85.4% for VILI, respectively [37]. VIAM does not have any added benefit over VIA [38]. Two RCTs on cervical cancer screening with VIA have been reported from India. The first RCT is a cluster RCT from South India wherein a single round of VIA screening was offered to the eligible women by trained nurses. The women were treated on the same visit, when appropriate. This trial reported a significant 25% reduction in incidence and a significant 35% reduction in cervical cancer mortality at the end of 7 years of follow-up [39]. The second RCT from Mumbai, India, investigated the efficacy of four rounds of VIA screening offered by trained primary health workers at 24-month intervals. This trial demonstrated a significant 31% reduction in cervical cancer mortality at the end of 12 years of follow-up [40]. Thus, VIA appears promising as a population-based strategy in the low-resource settings. Depending on the

Fig. 2. Positive VIA.
Fig. 3. Positive VILI.

availability of human resources, it may be used as a single-round or multiple-round screening approach as demonstrated in the two RCTs.

Recommendations for Cervical Cancer Screening

The current recommendations for cervical cancer screening by different societies from the more developed countries, i.e. the American Cancer Society (ACS) [41], the American Society for Colposcopy and Cervical Pathology (ASCCP) [41], the American Society of Clinical Pathology (ASCP) [41], the United States Preventive Services Task Force (USPSTF) [42] and the American Congress of Obstetrics and Gynecologist (ACOG) [43], for the general population are similar. It has been recommended that screening for cervical cancers with Pap smears is to be initiated at 21 years and continued every 3 years between the ages of 21–29 years. Thereafter, between the ages of 30 and 65 years, screening can be conducted every 5 years if cotesting with Pap smear is done or every 3 years if Pap smear screening alone is used. There is no need to screen women older than 65 years unless there was a diagnosis of cervical pre-cancer. Similarly, screening is not recommended for women that have undergone hysterectomies for a benign cause and who do not have prior history of cervical cytology higher than CIN2. For women who test negative on Pap smear but positive on HPV test, genotyping of HPV 16/18 and colposcopy only for women with positive results is recom-

mended. Alternatively, combined HPV and cytology testing may be repeated again within 12 months. The screening guidelines remain the same for women who have received the HPV vaccine. Women at high risk for cervical cancer may need to be screened more often.

These recommendations of cervical cancer screening are not applicable to less developed regions of the world where various logistics and feasibility challenges exist. Due to the high cost of setting up cytology-based screening programs, screening coverage is very low in low- and middle-income countries including India and hence, alternative screening methods need to be explored [44]. The alternative methods of cervix cancer screening like the VIA alone or triage of VIA-positive women with cytology appear promising. In the western world, the standard practice for cervical cancer screening is to screen women using cytology (Pap test) and refer the cytology-positive women for colposcopy and biopsy of the suspicious lesions. The diagnosis of CIN is based on histological confirmation and accordingly the subsequent treatment is planned. Though this strategy has been highly successful in reducing mortality in excess of 50% in many developed countries, it requires highly trained human resources and a substantial amount of laboratory equipment.

The 'screen-and-treat' approach is an alternative method in which the treatment decision is based on the results of the screening test or strategy (sequence of tests or triage for those with a positive first screening test result) and not on a histologically confirmed diagnosis of CIN 2+ unless an invasive cancer is suspected. Either of the tests, i.e.

HPV, cytology or VIA, may be used as screening tests. The women screened positive are treated with cryotherapy or large loop excision of the transformation zone (LEEP/LLETZ) ideally, immediately or soon for pre-cancer and women with invasive cervical cancer are appropriately referred for treatment. The 'screen-and-treat' strategy has certain drawbacks like overtreatment and its adverse effects, use of resources for treatment of a false positive screening test result, or no treatment (for a false negative screening test) and its consequences such as cervical cancer and related mortality, recurrence of CIN 2+, etc.

In Thailand, a single-visit approach of screening with VIA and treating with cryotherapy achieved higher coverage and revealed an increase in cervical cancer incidence rate. In Thailand, more than a million women in 20 provinces have been screened using a 'screen-and-treat' program with VIA and cryotherapy [45]. A demonstration project involving screening of women aged between 30 and 50 years with VIA and treatment with cryotherapy began in six African countries supported by the WHO, IARC, APHRC and project coordinators from the six African countries in September 2005. In this single-visit approach, 39.1% of clients were screened and treated on the same day. As a result of this demonstration project, the cervical cancer prevention services in these six countries have incorporated VIA and cryotherapy in their existing reproductive health services [46].

The WHO recommendation for low-middle-income countries is to ideally use a strategy of screen with an HPV test followed by VIA and treat. The other options are to screen with an HPV test and treat or to screen with VIA and treat. Screening with cytology followed by colposcopy

(with or without biopsy) and then treating is recommended only for countries where an appropriate, high-quality screening strategy with cytology followed by colposcopy already exists [44]. Cervical cancer screening programs will need to be developed or strengthened even in countries where HPV vaccine is introduced, as HPV vaccination does not replace cervical cancer screening [2].

Summary

The high disease burden of a preventable cancer of the uterine cervix is totally unwarranted. The magnitude of cases can be drastically reduced by concentrated prevention and control efforts in less developed regions of the world, including India. Some of the measures of primary prevention of cervical cancer include quitting tobacco, delaying the age at initiation of sexual activity to above 18 years, restricting the number of sexual partners and the use of condoms. HPV vaccination of the eligible population and early detection and treatment of cervical precancers with a single-visit 'screen-and-treat' approach appear promising for low-middle-income countries, especially for women living in rural and remote areas.

Acknowledgements

Source of support: NIL.

Disclosure Statement

The authors declare no conflict of interest.

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