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HPV: INFECTION, PREVENTION AND VACCINATION IN INDIA

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ABSTRACT: Cervical cancer (CaCx) is the fourth most common cancer among women worldwide. Infection of high risk Human papillomaviruses (hrHPV) is primary etiological factor for development of epithelial lesions in cervix ranging from warts to invasive cancer. CaCx is the second most prevalent cancer among females in India contributing to 14% of all cancers (NCRP, 2015). The persistent infection hrHPV (type 16 and 18) is responsible for more than 70% of cervical cancer, however, low-risk HPV i.e. type 6 and 11 causes approximately 90% of genital warts. Hence, preventive intervention for HPV infection may bring down the incidence of HPV associated disease including cervical cancers and genital warts. Primary prevention of cervical cancer can be achieved by vaccination and screening for hrHPV infection may act as tool for secondary prevention. Currently screening method includes visual inspection with acetic acid (VIA), cervical cytology, detection of HPV based on DNA and RNA. There is availability of p16 immunohistochemistry which as surrogate maker for hrHPV infection. Vaccines are now available for primary prevention which will reduce the burden of cancer; quadrivalent HPV vaccine (Gardsil®) targeting HPV type- 16, 18, 6 and 11 and bivalent vaccine (Cervarix®) against HPV type 16 and 18. This article is focussing on recent update on hrHPV and its association in Indian context.

KEYWORDS: cervical cancer, infection, high-risk HPV, prevalence, screening, vaccine

INTRODUCTION:

Cervical cancer (CaCx) is the fourth most common cancer among women worldwide [1] and second most prevalent in India contributing to 14% of all cancers [2]. HrHPV infection is well-established cause of epithelial lesions in cervix from warts to invasive cervical cancer [3]. More than 90% of invasive cervical cancer sample contain hrHPV -DNA [4, 5]. CaCx is one of the common and critical health issues among females in India, which is caused by persistent infection with hrHPV.

These are small non-enveloped virus that contain double-stranded DNA genome of 8 kb and can be classified as high-risk or low-risk based on the oncogenic potential of the various HPV genotypes [6-9]. Alone, high-risk HPV type 16 and 18 are responsible for about 70% of all CaCx cases worldwide [6-9]. Primary prevention of cervical cancer can be achieved by vaccination and secondary prevention by screening of hrHPV infection. Screening method include visual inspection after

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application of acetic acid (VIA), cervical cytology, detection of HPV infection based on DNA/RNA testing. HPV genotyping by polymerase chain reaction (PCR) with common consensus primer is also one of the available technique. The conventional method of screening by cervical cytology requires labour intensive, and a needs trained manpower for interpretation in view of clinical symptoms. Hence, alternate methods such as VIA, and HPV DNA testing have been developed with idea of objective criteria to compensate the paucity of trained manpower [10, 11]. The outcome from VIA quite sensitive but have low specificity, [12] while HPV DNA testing shows high sensitivity and specificity when compared with both as VIA and cervical cytology [13]. Few of the study [14, 15] have shown to provide effective immunity for cervical cancer which targeted HPV type 16, 18, 6 & 11.

Human papillomavirus

Human papillomavirus is a non-enveloped double stranded DNA virus [16] that infects skin and mucosae of upper respiratory and anogenital tract. Approximately 200 different HPVs have been characterized & new types are added and about 30-40 types of HPV are anogenital & 15-20 types are oncogenic [17, 18]. HPV viruses have been classified as 'high-risk' and 'low-risk' types based on their oncogenic potential and malignant progression of lesions [19, 20]. High-risk HPVs are type- 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. HPV types 16 and 18 were found high oncogenic and accounted for more than 70% of all cervical cancers and other most prevalent high-risk HPV types- 45, 31, 33, 52, 58 and 35 [19, 20]. Low-risk HPV types are mainly responsible for genital warts. HPV type 6 and 11 account for approximately 90% of the genital warts [18, 19] and recurrent respiratory papilloma [21].

HPV transmission and infection

HPV is the most common sexually transmitted infection and spread through oral, vaginal, or anal sex with infected person [22]. It can also spread through by vertical transmission from infected mother to child during pregnancy [23, 24]. Most of the hrHPV infections are acquired through sexual contacts and remains asymptomatic. In one of the study from USA which was evaluated the life time risk of getting hrHPV infection based on the number of sex partners concluded that average lifetime probability of getting infection of HPV in those who have at least one opposite sex partner is 84.6% (range, 53.6%-95.0%) for females and 91.3% (range, 69.5%-97.7%) for males.[25]Approximately 90% of incident infection of HPV in cervical sample is cleared spontaneously between up to 24 months including high risk types by immune system itself; however, persistent infection can only lead to the pre-cancerous changes [26]. The persistent infection by HrHPV leads to various stages of cervical dysplasia predominantly in superficial layer of squamous epithelium. These Squamous intraepithelial lesions (SILs) are sub-classified into two main, low-grade squamous intraepithelial lesions (LSIL) and high-grade intraepithelial lesions (HSIL), group based on cyto-morphology. LSIL, in cytology, is probable representative of cervical intraepithelial neoplasia (CIN) 1 and HSIL is of CIN 2 or 3 [27].

HPV associated cervical cancer in India

According to one of the study, annually 122844 new cases of cancer are being diagnosed and 67477 deaths are attributed to cervical cancer in India. [28]. The peak age of cervix cancer incidence in India is 55 to 59 years [29]. The common histological type of cervical cancer is squamous cell carcinoma (SCC) 70 to 80% in ectocervix [30]. In paucity of centralized HPV screening program the regional studies depicts variable percentage of HrHPV prevalence in women. [31, 32]

Multiple risk factors are involved in carcinogenesis of cervical cancer. Epidemiological data suggests that sexual, reproductive factors, socio-economic and lifestyle factors such as diet, smoking, & use of oral contraceptives are few of the responsible factors for occurrence of cervical cancer [33-37]. Cervical cancer is preventable by preventing and screening of hrHPV infection, which in turn leads to cancer. Hence, vaccination & screening are important screening tools. High risk HPV type 16 and 18 are most prevalent and account for 76.7% of cervical cancers in India [38].

Prevention of cervical cancer

The effective method for cervical cancer prevention would be combination of both vaccination & screening depending on the age group. In one of the study [39] few strategies have been suggested to prevent HPV infection which, includes sending counselling messages, male circumcision, having selective partners, and delaying first intercourse. These methods are more effective to prevent of HPV and other sexually transmitted disease and reduces risk of CaCx. Micronutrients and supplements also help to reduce risk of HPV infection, persistence, progression and regression [39]. Secondary prevention by screening includes Pap stain based on cyto-morphological abnormalities of cervix, helps in reducing CaCx incidence and mortality by 80% in developed countries [40]. High-risk HPV DNA test, based on DNA-RNA hybrid complex formation, also helps in reducing burden of infection and incidence of CaCx. It is US-FDA approved and validated tests and is commercially available for HPV screening.

HPV vaccines

HPV vaccination is one of the robust and promising methods for prevention. HrHPV type 16 and 18 is the most common cause of cervical cancer while, low risk HPV type 6 and 11 is for genital warts among women worldwide. HPV vaccines are now commercially available and helping to reduce the burden of cervical cancer and also anogenital cancers [41]. HPV vaccines have been developed based on viral capsid proteins L1 These L1 Virus like particles (VLPs) are morphologically and antigenically similar to HPV but lacks genomic DNA, however provide effective immunity if given before the exposure of HrHPV [42]. The suggested age is 9-13 years in three doses. There are two HPV vaccine licensed globally and commercially available. The quadrivalent vaccine Gardsil® (Merck and Co. Inc., USA) that contains purified L1 VLPs of HPV type 6, 11, 16 & 18. It is delivered by intra-muscular injection in a three shot immunization protocol at 0, 2, and 6 months. A bivalent vaccine Cervarix® (GSK, Belgium) that contains purified L1, VLPs of HPV types 16 & 18 and it is also delivered by intramuscular injection in three shot immunization protocol. The three dose regime of vaccine provides protection of 8.4 years (for bivalent) and 5 years (for quadrivalent vaccine) [42]. To improve the efficacy of the protection the research is also directed to develop a 9 valent vaccine [42, 43]. In India, both HPV vaccine have been licensed and are under trial. The effectiveness and duration of vaccine protection may be affected by the socio-cultural pattern of the region which eventually decides the age of first HPV exposure through sexual norms. Thus, vaccination of sexually active females of any age is recommended. However, in male, HPV vaccination is still an under-explored though a necessary domain. The world health organization (WHO) recommends an organized the national immunization program worldwide for HPV vaccination and given to 9-13 years old girls, prior to first coitus. The Indian academy of paediatrics committee on immunization (AIPCOI) also recommends HPV vaccine to all females who can afford the vaccine between ages 10-12 years [44].

CONCLUSION:

Being an infective aetiology, CaCx has the potential of reduction in the incidence and prevalence of by the active intervention, in the form of prevention of spreading of HPV infection and through cervical screening program. The methods adopted for this goal may be personalized and community based. The coverage of screening is patchy and non-uniform due to multiple reason which poor infrastructure and awareness. The WHO recommends that routine HPV vaccination should be included in national immunization program. The cost of vaccine is one of the limiting factor for its inclusion and implementation as national immunization schedule, however the vaccine will have a long term effect on our economy in the form of reduced disease burden. Few more researches, focussed on more effective vaccine(9 valent vaccine) development are under process, which may improved overall survival and benefit to the women[42].

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