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Potential opportunities to reduce cervical cancer by addressing risk factors other than HPV

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Cervical cancer is the most common cancer in developing world and 80% of global burden is reported from these nations. Human papillomavirus along with poverty, illiteracy/lower education level and standards, multi-parity, tobacco, malnutrition and poor genital hygiene may act synergistically to cause cervical cancer. Risk factor of cervical cancer may in itself be the reason for non-viability of cervical cancer vaccine program in this part of the world. Interventions to address these risk factors in addition to vaccination of girls before their sexual debut may hold promises of reducing the morbidity and mortality of female genital cancers.

Keywords: Cervical cytologic screening, Developing countries, Gynecologic cancers, HPV typing, HPV vaccine

In 2008, >85% of the 5,30,000 global new cervical cancer cases and about 88% of 275000 deaths occurred in resource-constrained developing countries [1]. Maternal, newborn, and child mortality, along with a broad array of vaccine-preventable and other communicable diseases, also remain urgent concerns in these less developed regions of the world [2]. Cervical cancer, although a chronic disease of sexually active women, is the product of infection, poor hygiene, poverty, high parity and malnutrition [3,4]. Approximately 40 of more than 150 human papillomavirus (HPV) types identified can infect uterine cervix after (co-)transmission through sexual contact. HPV is a not only leading but also un-recognized sexually transmitted disease as vast majority of sexually active women and men have been infected with HPV at least once in their lifetime without any specific discern signs and symptoms and most of these infections clear spontaneously within few years time. However, persistent infections with one of approximately 14 carcinogenic (high-risk) HPV types are responsible for nearly all cases of cervical cancer. Most of these high-risk types are phylogenetically related to either HPV 16 (31, 33, 35, 52, and 58) or HPV 18 (39, 45, 59, and 68) [5].

Periodic/regular national cytology based cervical cancer screening program has been shown to be consistently successful in substantial reduction of cervical cancer incidence [5]. The novel anti-cancer vaccine provides more than 90% type specific protection against HPV 16 and 18 to an uninfected subjects immunized between the ages of 9–26 years [6]. Wheeler et al. [7] have also demonstrated the cross-protective efficacy of HPV 16/18 AS04-adjuvanted vaccine against 6 month persistence infection by four oncogenic non-vaccine HPV types—HPV 33, HPV 31, HPV 45, and HPV 51.

In recent years, prevention of cervical cancer has mostly centered on periodic cervical exfoliated cytologic evaluation at regular interval and detection of HPV DNA or RNA in cervico-vaginal cytological or tissue specimen [5]. Vaccination of young females between 9 and 26 years of age before the sexual debut against two strains of HPV 16 and 18 has recently emerged as yet another as well as popular mean of preven-

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tion of cervical cancer and is gaining wide popularity around the world. In some circumstances vaccination against HPV 16 and 18 has been projected as an alternative solution to the problems associated with cervical cytological screening [8,9]. However, considerable variation in both age-standardized HPV prevalence and HPV type distribution between population and geographical region across the world hampers universal administration of vaccine against HPV 16 and 18 [10]. HPV vaccines are very expensive and unaffordable for many public health initiatives in developing countries [11].

The time of sexual debut of individual is influenced by social, cultural, behavioral, biological circumstances and is mostly unpredictable. Prevalence of HPV infection peaks between the ages of 20 and 25 years as a result of infection by and clearance of virus in years following average age of first sexual intercourse in the population. Although the prevalence of HPV infection declines with age of women, older women continue to be at high-risk of acquiring new infection with other oncogenic HPV and prevalence of cervical cancer has a long drawn-out peak after the age of 35 years [5]. This indicated that sexually active women are at significant risk of HPV infection and subsequent cancer throughout their lives. Efficacy, immunogenicity and safety prolife of HPV vaccine has been established for maximum period of only 6.4 years based on randomized controlled trial conducted in just three countries [6]. Cross-protection against 6 months persistence infection by four non-vaccine oncogenic HPV type has been documented with mean follow-up of less than 35 months [7]. As per available scientific evidence, if vaccination is included under expanded program of immunization for all adolescent girls, the immunized subjects are unprotected both at time of peak of HPV infection prevalence and during periods of infection with high-risk type. Additionally, HPV vaccine need to be stored between 2°C to 8°C and authorisation and perpetuating of storage cold chain of the vaccine in the developing countries is refutable for the time being [12]. Because of the above mentioned reasons, HPV vaccination does not eliminate the need for cervical cytological screening (CCS) of the vaccinated.

Decreased cervical cancer morbidity and mortality of Papanicolaou cytology observed over past 50 years in high-income countries has not been emulated in many middle-income countries [8]. Shortage of both auxiliary and technical staff is most commonly reported challenge in developing regions of the world [13]. Auditing of the sampling technique, training cytotechnicians, identifying and monitoring HPV prevalence pattern, securing chain of communication is unattainable in the capacity limited zones. Apart from colossal cost, the other disadvantages of CCS include technical difficulty of sampling high cervical canal, false negative rate of up to 45% [14,15].

Approximately 14 carcinogenic HPV types are literally responsible for all cases of cervical cancer. HPV viruses are phylogenetically related and there exists chances of HPV testing to cross react with non-oncogenic. Hence, HPV testing has an apparently unavoidable trade-off between sensitivity and specificity. Optimization of clinical specificity of HPV testing while maintaining its sensitivity for detecting cervical intraepithelial neoplasia 3 worse (CIN 3+) requires careful choices about which HPV types are targeted and the threshold for a positive result. First and foremost prerequisites to have HPV testing with reasonable sensitivity and specificity are derivation of detection threshold and optimization of clinical specificity of HPV testing. Population-based survey to detect the commonly prevalent high-risk HPV type within each geographical region and country followed by inclusion of only prevailing HPV type in HPV testing and subsequent validation of HPV testing is necessary before we can report the results of HPV testing with reasonable accuracy to guide the policy decisions. Commonly used HPV tests have not completely optimized the threshold for positivity in cervical screening of general populations [5]. Severely limited resources and multiple HPV type will make all notions of validation of HPV testing/assay an absurd in developing countries.

Persistent HPV infection is a necessary, but not sufficient, cause of cervical cancer. High parity, poverty, poor sexual hygiene, never schooling, multiple sexual partners, tobacco smoking, co-infection with human immunodeficiency virus, Herpes simplex virus type 2 and Chlamydia trachomatis, immunosuppression, oral contraceptive use and dietary deficiencies of vitamin A are all co-factors that are necessary for progression from cervical HPV infection to cancer [3,4]. These co-factors are none, but the un-addressed prevailing public health issues in the undeveloped sectors of the world. Reducing poverty, improving the standard of living, achieving universal education, increasing investments in program aimed at preventing the development of unhealthy life behaviors and improving access to family planning methods can have immense medical, social and economical impact on these resource-constrained developing nations and far greater consequence of decreasing morbidity and mortality not only of cervical cancer but also of many preventable communicable and non-communicable human ailments. Intervention to reduce the occurrence of these non-HPV risk factors of genital malignancies may have profound impact on incidence of gynecologic cancers in developing countries. In addition to vaccination, efforts must be directed towards amelioration of the aforementioned risk factors of gynecologic cancers.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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