HPV and Cervical Cancer – Prospects For Prevention Through Vaccination

NEETA SINGH

SUMMARY

Cervical cancer is one of the most common cancer and is a leading cause of cancer related death in women. Sexually transmitted human papilloma viruses (HPVs) play a central role in its etiology. There are more than 100 different HPV types. 38 types infect the genital tract, fall into 2 categories – low risk and high risk types. High risk HPV-16 is detected in 50-60% of cervical cancer followed by HPV-18 (10-12%). HPV vaccines, both prophylactic and therapeutic are in Phase III and Phase II clinical trials respectively. Prophylactic vaccines against HPV-16 and 18 induce the generation of neutralizing antibody to the virus coat protein and have shown promising results but will be effective pre-exposure to virus. Therapeutic vaccines are aimed at eliminating existing infection by induction of a strong cell mediated response. However, the unanswerable questions are how well a prophylactic vaccine will be accepted and how extensive the coverage will be?

WHAT IS HPV?

It is a double stranded circular, epitheliotropic DNA tumor virus. Over 100 different HPV types are known, they are classified according to DNA sequence using the L1 open reading frame of the genome. HPVs are classified into types, subtypes and intratypic variants. HPV types are >10% unlike the other, sub types differ by 2 to 10% and the variants differ by 1 to 2% in coding region and 5% in non coding region of viral genome. HPVs infect different areas of the skin. HPV enters the body through the mucosal membranes and does not spread systematically. HPV does not circulate in blood but is localized to the site affected. It cannot be grown in vitro, in culture. HPV testing involves testing for HPV DNA in patient samples. The HPV genome is 7900 bp and is divided into 3 functional regions 1) non coding upstream regulatory region – late control region (LCR) 2) early region consisting of open reading frames (ORFs) E1, E2, E4, E5, E6, E7 which are involved in viral replication, transcription and oncogenesis and 3) late region encoding the L1 and L2 structural proteins of the viral capsid. The E6 and E7 genes code for proteins that inactivate tumor suppressor genes such as p53 and Rb. Whereas, L1 gene codes for a protein that self assembles into the shell (capsid) of the virus. Empty shells (capsids) are called virus like particles (VLPs).

The consequence of genital HPV infection of greatest public health importance is development of high-grade cervical intraepithelial neoplasia (CIN) and subsequently, cervical cancer. The clinical diagnosis includes genital warts for the low risk HPV types 6, 11 whereas the pathological diagnosis for intraepithelial lesions include cervical intraepithelial neoplasia (CIN) including carcinoma in situ (CIS). The intraepithelial lesions at other genital sites involve the vagina, vulvar, penile and the anal region. 38 genital HPVs are known. They are low risk types such as HPV 6, 11, 40, 42, 43, 53, 54, 57, 66, 84 which lead to genital warts and low grade CIN, but the cancer potential is low/negligible. However, the high risk HPV types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 55, 56, 58, 59, 68, 73, 82 and 83 cause low grade CIN, high grade CIN and invasive cancer, and thus have high...
cancer potential. The HPV type most prevalent globally is HPV-16, which is found in 50 - 60% of cervical cancer, followed by HPV-18 found in 10 - 12% of cervical cancer. Geographical variation is seen in the distribution of other HPV types. Epidemiological studies of genital HPV suggest that it is one of the most common STDs. HPV transmission is influenced by sexual activity and age. It has a predilection for stratified squamous epithelium. 75% of sexually active adults are likely to be infected with at least one HPV type. However, vast majority of infections resolve spontaneously. Only minority (<1%) of HPV infections progress to cancer. As with other sexually transmitted infections, HPV causes more problems for women than for men. The lifetime risk for genital HPV is 50 to 80% and for genital warts ~5%. For women participating in routine screening, the risk in the abnormal Pap smear subjects is 35%, for CIN it is approximately 20% and for invasive cervical cancer it is <1%. However, in women without routine screening the risk for cervical cancer is up to 4%.

CERVICAL CANCER

It is the 5th most common cancer in humans, and the 2nd most common cancer found in women after breast cancer. The worldwide incidence is 5,10,000 new cases annually, with India accounting for 1,32,000 cases. The mortality rate from this cancer is 2,88,000 worldwide and 74,118 deaths occur per annum in India. The incidence rate rises in 30-34 years age group and peaks at 55-65 years. The median age of women with cervical cancer is 38 years (age range 21-67 yrs). All humans are at risk of developing the disease, but several factors can increase the risk. The risk factors for cervical cancer are viral infections (HPV, HIV, HSV), multiparity, early initiation of sexual activity, multiple sex partners, smoking, low socio-economic status, diet low in antioxidants and poor hygiene, long term use of oral contraceptives and immune suppression like after renal transplant, etc. Pap test is used to find cellular abnormalities in cervical tissue that may become cancerous. The earlier it is diagnosed the better the cure rate. Majority of women become infected with HPV at some point in their lives, usually soon after onset of sexual activity. Most cervical cancers arise at the squamo-columnar junction and transformation zone between the columnar epithelium of the endocervix and squamous epithelium of the ectocervix where there is continuous metaplastic change. Since maximum metaplastic activity occurs at puberty and first pregnancy between 18-30 yrs of age, hence detected during active sexual life. HPV, a sexually transmitted virus is the most important etiological agent. Recent studies have shown that even using condoms cannot completely protect against HPV as the virus is passed from person to person by skin to skin contact and the skin in the genital area may not be covered by a condom. The infection is cleared by the host immune system in 6-12 months. The regression is inversely related with CIN grade. Persistence of infection is more with high risk HPV types and is necessary for progression to cancer, though the latent period between infection and actual progression to cancer can be 10 years. The persistence of HPV is related to host and viral factors. Continuous expression of E6, E7 genes of HPV in cycling cells, integration of virus into host genome, inactivation of E2 gene due to viral integration/mutation, host factors such as HLA genotype, polymorphism of cellular genes, secondary genetic changes and HPV sequence variation. HPV is necessary but not sufficient for progression to cancer. The frequency of HPV is 0-80% in normals and 99.7% in cervical cancer. The carcinogenic process is linked to activities of four multifactorial viral proteins E1, E2, E6 and E7. HPV DNA is frequently integrated into host genome in cancer, leading to inactivation of E2, resulting in E6 and E7 overexpression. E6 and E7 are involved in activation of oncogenes and inactivation of tumor suppressor genes. E7 protein acts in concert by binding and activating the function of Rb and related proteins. It overcomes block of pRb, liberates E2F transcription factors and thus plays a key role in promoting host cell and viral DNA synthesis. It binds and activates cyclin complexes CDK2 and thus controls cell cycle progression. E6 on the other hand abrogates p53 transcriptional activity, causes p53 degradation by ubiquitination via the proteosome pathway.
It interacts with other cellular proteins and activates telomerase leading to indefinite cell division. Hence, HPV E6 and E7 genes are involved in activation of oncogenes and inactivation of tumor suppressor genes. Transcription of E6 & E7 is controlled by promoter and enhancer elements in the LCR, which contains several E2 binding sites, in addition to binding sites for several cellular transcription factors.

The incidence of cervical cancer in different countries may be associated with distribution of specific viral variants. HPV 16 and 18 have a number of variants each with different geographical distribution, some associated more often with invasive neoplasias. Sequence analysis showed that they form 5 phylogenetic clusters. HPV 16 – Asian American variants (AA), African variants (AF), Asian variants (AS), European (E) and North American (NA). The sequence variation/ or mutation after HPV infection may modify the function of the encoded protein and viral assembly. Screening for precursor lesions is one of the most successful public health measures in prevention of cervical cancer. The commonly used screening techniques include cytology – pap smear, cervicography, colposcopy and testing for HPV. Early detection of cervical neoplasia allows interventions like: conization, cryocautery, laser vaporization, loop electrosurgical excision and hysterectomy

HOW CAN HPV BE PREVENTED?
Currently, HPV infections cannot be prevented; except by abstinence and lifetime mutual monogamy. HPV is a sexually transmitted virus. Some specific characteristics of HPV infection make it a different target for intervention by “Safe sex” education campaigns. There is no clear evidence as yet that barrier methods of contraception, most notably use of condoms, confer a protection against HPV infection. Secondly, except for genital warts, the infection is asymptomatic. Only trying to intervene on the factors, which facilitate persistent HPV infection, will be beneficial.

CAN A HPV VACCINE HELP?
Various strategies have been designed to develop vaccine against HPV that could prevent viral infection and thus, cervical cancer development. In the case of HPV, it is not possible to prepare traditional vaccines in a conventional way, since there are still no efficient means to quantitatively produce viral particles.

Prophylactic vaccines offer strong promise for prevention in future. A vaccine that prevents persistent infection with HPV will protect against subsequent development of cervical cancer. The bivalent Glaxo Smithline prophylactic vaccine targets two types of HPV infection – HPV 16 and 18. This vaccine contains man-made virus – like particles (VLPs) that look just like HPV 16 and HPV 18. Unlike the real HPV 16 and HPV 18 viruses, the VLPs are empty shells which are non-infectious, but are very immunogenic. The body’s immune system responds to the VLPs as it would to the real HPV 16 and 18 viruses – producing antibodies and other defenses. These defenses protect against infection with HPV 16 and HPV18, resulting in lasting immunity. Women in a small pilot clinical trial who were given the vaccine developed immunity to persistent infection with HPV 16/18 and tolerated the vaccine well. Merck has developed a quadrivalent prophylactic vaccine against HPV 16/18/6/11. This vaccine is L1 VLP protein expressed in yeast. They studied the effect of the vaccine in 1533 subjects (768 vaccine and 765 placebo recipients), with a median age of 20 yrs. They found 41 cases of HPV 16 infection and CIN, 32 cases of HPV 16 infection, 5 cases of HPV 16-CIN 1 and 4 cases of HPV 16-CIN 2/3 in the placebo group. Whereas, the vaccine treated group showed 100% efficacy. The ongoing HPV vaccine study has begun phase III trials with this vaccine which offers potential elimination of up to 70% of invasive cervical cancers, 60% of high grade CIN and 90% of genital warts. Future HPV immunization programmes plan to target 9 to 12 years olds, adolescents and young adults. As for protection in men - data on HPV vaccines in men is not yet available. However, the major implementation issue is societal acceptance of vaccines. The promise of such vaccines will be realized only if immunization programmes achieve wide coverage.
Therapeutic vaccine studies are ongoing on therapeutic vaccines which aim at eliminating existing infection. These are targeting the E6 and E7 proteins of HPV 16. Therapeutic vaccines for HPV have been based on peptides, proteins, chimeric proteins, DNA, viral vectors, bacterial vectors, dendritic cells, and modified tumor cells. They are intended to stimulate the immune system against E6 and E7 early viral antigens. One major limitation however, is the fact that the existing alterations in most tumors will possibly prevent the efficient use of these vaccines.

Some important issues that must be considered are – duration of protection induced by these vaccines? Prophylactic vaccines will be effective pre-exposure to virus and hence the target population for vaccination will be 9-10 year old pre-pubertal girls – this will raise cultural and social issues? Will we need different cocktails of HPV types for different population? If we control the current common types, will other rarer types take their place? Although results in the development of vaccines against HPV are promising, it will be a decade or more before they become available worldwide and are cost effective. Routine screening should continue to detect and treat women who are infected prior to vaccination or with other HPV types not covered by the vaccine.

REFERENCES:

KGMC Travel Fellowship

Indian Society of Medical & Paediatric Oncology invites application for KGMC Travel Fellowship. The total award amount is Rs. 2500-00 (to cover their travel and stay). There are two fellowships each year. Candidates are expected to spend 2 weeks at a major cancer centre in India. On completion, they have to submit one page visit report. Awarded candidates should correspond with the host institute to finalise their dates of visit and stay arrangements. Interested applicants may send their brief CV to

Dr Purvish Parikh
Secretary
Indian Society of Medical & Paediatric Oncology
Professor & Head
Department of Medical Oncology
Tata Memorial Hospital
Parel, Mumbai-40 0012