

Human Papilloma Virus (HPV) and Cervical Cancer

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Cervical cancer is the second most common cancer among women globally, with an estimated 493,000 new cases diagnosed annually. About 274,000 of these women will unfortunately die of the disease every year. Some 83% of the cases occur in developing countries, where cervical cancer accounts for 15% of female cancers, with a risk before age 65 year of 1.5%, while in developed countries it accounts for only 3.6% of new cancers, with a cumulative risk (ages 0-64) of 0.8%. The highest incidence rates are observed in sub-Saharan Africa, Melanesia, Latin America and the Caribbean, South-Central Asia and South East Asia. In South Africa, about 7000 women will develop cervical cancer annually, of which about 4000 will die from the disease. It is the most common cancer in Southern

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African black women, accounting for about 32% of all cancers in this group of women. The lifetime risk of cervical cancer amongst South African women is about 1 in 26.

140 HPV subtypes

Infection with oncogenic HPV types is a necessary cause of cervical cancer and 99% of invasive cervical cancers are associated with high risk HPV types. The HPV is a double stranded DNA virus of which there about 140 subtypes. About 40 of these viruses will infect the anogenital region. Twenty of these subtypes that are known to infect the anogenital region are regarded as high risk in that if their infection is left alone, it will progress to invasive cervical cancer. Subtypes 16,18,31,33,35,45,51,52,56,58,59,68 are regarded as the most commonly encountered high risk types and are most commonly associated with the development of cervical cancer. HPV16 and 18 are responsible for about 70% of cervical cancers. The next 8 HPV subtypes mentioned above account for a further 15-20% of cervical cancers so that about 90% of all cervical cancers are in fact due to 10 HPV subtypes. The remaining 20, of the 40 HPV subtypes that are known to infect the anogenital region, are regarded as low risk. Infection by these subtypes is most unlikely to cause cervical cancer but is overwhelmingly responsible for the development of anogenital warts. These include HPV subtypes 6,11,40,42,42,44,54. HPV subtypes 6 and 11 account for about 90% of anogenital warts. In summary, HPV subtypes 16 and 18 cause about 70% of cervical cancers, about 50% of the high grade SIL lesions and about 25-30% of the low grade SIL lesions, whilst HPV types 6 and 11 are associated with about 15% of the low grade SIL lesions but with about 90% of anogenital warts. HPV subtypes 31,45,33,35,51,52,55,58 are responsible for a further 15-20% cervical cancers.

Risk of infection

HPV is a common infection, seen overwhelmingly in sexually active women and has an estimated global prevalence rate of about 70% by 50 years of age. Most infected individuals will however eliminate evidence of the virus without ever developing clinically recognised manifestations. The highest risk of infection occurs in adolescents 15-19 years of age, with a five-year cumulative risk of 42.5%, decreases with age, but there still is a 12.5% cumulative risk in women > 45 years of age. It is important to remember that once sexual activity has commenced and whether one is in a monogamous relationship or not, the risk of infection remains throughout life. Epidemiologic estimates suggest that the worldwide prevalence of HPV infection is 9-13% and that about 630 million people are infected annually. Early age of first coitus, increasing number of sexual partners and smoking all increase the chances of infection and the likelihood of cervical cancer.

Squamous intraepithelial neoplasia

Although HPV infection is frequently transient, especially in young women, with about 80-90% of infections clearing within 24-36 months, persistent infection of the cervix with high risk HPV types is strongly associated with the development of squamous intraepithelial neoplasia and cervical cancer. The life cycle of HPV is dependent on active cellular replication and subsequent cellular division. Because the uppermost layers of the squamous epithelium of the cervix have undergone terminal differentiation and are no longer dividing, HPV requires access to the undifferentiated basal layer of the epithelium to initiate a productive infection cycle. Current hypothesis suggest that HPV accesses the underlying basal layer of the cervix through naturally thin epithelial layers, such as those found in the transformation zone of the cervix, or through micro abrasions in the epithelium of the cervix produced during sexual activity. Once infection has been established, the virus uses host cell machinery to replicate viral genetic material and express viral proteins. Because viral replication is dependent on continued cellular division, the virus has evolved to express proteins, E6 and E7, which inhibit cellular differentiation by inhibiting the P53 suppressor gene and the retinoblastoma gene respectively. This will primarily result in continued cellular proliferation, desegregation of the chromosome during mitosis, accumulation of aberrant genetic material, impaired apoptosis and over years the accumulation of abnormal cells and ultimately the occurrence of low grade SIL, high grade SIL and finally invasive cervical cancer. Unrestricted cell growth is therefore the landmark of HPV infection and many HPV-associated clinical manifestations can be explained by these molecular mechanisms. There is abundant data provided by the International Agency of Research in Cancer which supports that HPV is strongly associated with cervical cancer whatever the background incidence of cervical cancer is for the country. Pooled odds ratio for invasive cervical cancer

associated with the presence of any HPV type is 158. HPV is overwhelmingly the causative agent of cervical cancer and even though the worldwide prevalence of high risk HPV types in cervical cancer shows geographic variation in contribution made by the different HPV types to invasive cervical cancer, the reality is that types 16 and 18 will account for about 70% of the cases and that HPV types 31,33,35,45,52,58 are the next most common globally. Recently, it has been reported that the risk of developing SIL or invasive cancer 10 years after the HPV infection is about 17% for HPV 16 and 13.5% for HPV 18. Exposure and persistence are more frequent with HPV16 than with the other HPV types.

Cervical cancer affects young women

Because cervical cancer affects young women, it is an important cause of lost years of life in the developing world and is responsible for about 2.7 million years of life lost (YLL) worldwide annually. It is the biggest single cause of YLL from cancer in the developing world. Yet its impact is not restricted to the developing world only. Even in the developed world, a woman dying from cervical cancer loses an estimated 26 years of life compared with 19 years of life for breast cancer and 17.6 years of life if dying from ovarian cancer.

HPV vaccines

The recent development of the HPV vaccines to combat the impact of HPV on the cervix has the potential to significantly decrease the incidence of cervical cancer globally. The development of prophylactic vaccines against HPV over the last 10 years has followed the discovery of the technology to produce VLPs or virus like products. The vaccines are formulations of the major capsid L1 proteins of the natural HPV particle. L1 monomers in yeast, insects or mammalian cells self assemble into the VLPs which closely mimic the structure of the natural HPV virions and are devoid of HPV genome, namely, they are not toxic, don't contain infectious

genetic material, are not oncogenic and don't have disease producing potential. Administration of these vaccines to patients will produce neutralising antibodies which bind to natural HPV virions, preventing the entry of the HPV into cervical cells. At present there are two multivalent vaccines which have been used in a number of large studies. The one vaccine is formulated to protect against HPV 16 and 18, while the other is formulated to protect against HPV types 6, 11, 16 and 18. Ideally the vaccine should be given prior to sexual activity, although sexual activity, a previously abnormal cervical smear or a positive HPV screening test does not exclude the patient from getting the vaccine. Vaccines that prevent viral diseases, such as polio, measles, smallpox and hepatitis B have provided some of the most successful strategies

to reduce infectious- disease associated morbidity and mortality. Prophylactic vaccination has reduced the incidence of hepatitis infection by 72%, for measles, diphtheria and rubella by 99.9% and has almost completely eradicated polio and smallpox. The fact that cervical cancer is caused by high risk HPV types provides an exceptional opportunity to use vaccination as a tool for cervical cancer prevention. This national strategy to combat cervical cancer has been shown conclusively to be very effective in all the published studies....the HPV vaccines are very well tolerated, highly immunogenic, highly effective and associated with significant protection against development of cervical cancer. In line with the fact that we have failed so dismally in combating cervical cancer globally, the concept of having a vaccination programme that is most effective in preventing its occurrence is exciting and inspiring.

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References on request

