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Review Article

The Burden of Disease Associated with Infection with Human Papillomavirus

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ABSTRACT

Human Papillomavirus is associated with a significant burden of disease globally, particularly with cancer of the cervix, for which persistent infection with high-risk types of HPV is necessary for the development of cervical cancer. Other cancers associated with HPV infection, particularly with HPV 16, include cancer of the vulva, vagina, penis, anus and some head and neck cancers. Globally approximately 600 000 cancers can be attributed to HPV infection. The advent of two commercially available vaccines had provided a new paradigm for the prevention of infection with HPV, particularly HPV infections associated with cancer.

Keywords : Human Papillomavirus (HPV), infection, cancer

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INTRODUCTION

Over a 150 different types of Human Papillomavirus (HPV) have been identified, of which about 40 are known to infect the anogenital tract. HPV's are DNA viruses that infect cutaneous and mucosal epithelia, manifesting as non-genital or genital warts, and preinvasive and invasive lesions. HPVs infecting the anogenital tract are divided into high-risk and low-risk types, based on their association with malignant or benign disease. HPV infection is associated with almost all cervical cancers, but also with other cancers of the anogenital tract including cancer of the vulva, vagina, anus, penis and some head and neck cancers.

CANCER OF THE CERVIX

Cancer of the cervix is the commonest cancer found among women in the developing world, where more than 80% of all cases are diagnosed. In 2002, there were an estimated 493 000 new cases and 274 000 deaths from cervical cancer[1]. The highest incidence rates of cervical cancer are observed in sub-Saharan Africa, Melanesia, Latin America and the Caribbean, South Central Asia, and South East Asia[1].

There is now a considerable body of epidemiological, clinical and molecular evidence that persistent infection of the cervix with high-risk types of HPV is necessary for the development of cervical cancer. High-risk types of HPV are identified in nearly all carcinomas of the cervix and the relative risk of cervical cancer associated with infection with high-risk types of HPV is higher than the risk of lung cancer associated with smoking[2]. Munoz et al.[3] pooled data from 11 case-control studies involving 1918 women with histologically confirmed squamous cell carcinoma (SCC) of the cervix and 1928 control women. The pooled odds

ratio for cervical cancer associated with the presence of any HPV was 158.2 (95% CI: 113.4 – 220.6). On the basis of the pooled data, fifteen HPV types were classified as high-risk types (16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) and are considered carcinogenic.

In a meta-analysis of HPV types found in invasive cervical cancers worldwide[4], data on a total of 10 058 cases (which included SCC, adenocarcinomas (ADC) and adenosquamous carcinomas) confirmed the high prevalence of HPV in cervical cancers in different regions of the world, with HPV 16 (51%) and 18 (16.2%) being the commonest. However, more than 16 other types of HPV were also associated with cervical cancer, of which types 45, 31, 33, 58 and 52 were the most prevalent. Further, HPV type 16 was more prevalent in SCC and HPV type 18 more prevalent in ADC of the cervix. Overall, HPV prevalence differed little between geographical regions (83 – 89%) but was low compared to the almost 100% prevalence in studies that have used the most sensitive methods of detection for HPV[4].

There is good evidence that HPV infection precedes the development of cervical cancer by a number of decades and that persistent infection with HPV is necessary for the development of and progression of pre-cancerous lesions of the cervix, either to higher grades of pre-cancerous disease or to cancer[5].

The natural history of cervical cancer offers two important opportunities for prevention: 1] primary prevention by preventing HPV infection ab initio and 2] secondary prevention through the detection of pre-invasive lesions of the cervix, removing them and thus preventing progression to cancer.

Primary Prevention

The development of vaccines against certain types of HPV has been a major breakthrough in the options available for the prevention of cervical cancer. Monovalent (against HPV 16), bivalent (against HPV 16, 18; Cervarix, GlaxoSmithKline Biologicals, Rixensart, Belgium) and quadrivalent (against HPV 6, 11, 16, 18; Gardasil, Merck and Co.,Inc, West Point, Pennsylyania, USA) vaccines have been tested in randomised placebo-controlled trials and shown to be safe, immunogenic and highly efficacious up to 6.5 years after vaccination. The vaccines use HPV type-specific L1 proteins that self assemble into Virus-Like Particles (VLPs). In the bivalent vaccine, the L1 protein of each type is expressed via a recombinant baculovirus vector. The vaccine consists of purified L1 VLPs of HPV types 16/18 formulated on a ASO4 adjuvant comprising 500μg of aluminium hydroxide and 50 μg of 3-dacylated monophosphoryl Lipd A. The vaccine is delivered by intramuscular injection at 0, 1 and 6 months.

In the quadrivalent vaccine, the L1 protein for each HPV VLP type is expressed via a recombinant Saccharomyces pombe vector and the vaccine consists of purified L1 VLPs of HPV types 6/11/16/18 formulated on a proprietary alum adjuvant. The vaccine is also given via intramuscular injection, at 0, 2 and 6 months.

Both vaccines work by inducing neutralising serum antibodies (IgG). Studies consistently show that L1 VLPs induce high levels of serum neutralising IgG, that is presumed to transudate across the cervical epithelium, in high enough concentration to bind to virus particles and prevent infection.

There is good evidence provided by randomised placebo-controlled trials that these vaccines prevent both persistent infection with the types included in the vaccines, as well as pre-invasive lesions of the anogenital tract associated with the types present in the vaccines. In addition, the quadrivalent vaccine prevents the development of genital warts caused by types 6 and 11[6-12].

Both vaccines appear to offer full protection against types 16 and 18, which are estimated to cause over 70% of cervical cancers worldwide, and a slightly lower fraction of cervical cancer precursors. There are some data that the immune response to vaccination

against types 16 and 18 provides some cross protection against types 45 and 31, both important in the etiology of cervical cancer, thus increasing the projected protection from vaccination to 75 – 80%.

Both vaccines however are prophylactic and should be administered to individuals prior to infection. HPV is transmitted through skin-to-skin contact, and this most commonly occurs with sexual activity. Thus the vaccine should ideally be administered to girls (and possibly boys) prior to the onset of sexual activity, which varies considerably from country to country and in different cultures. Vaccination of girls aged 9 – 12 years of age with high coverage is most likely going to be the most clinically effective and cost effective strategy for cervical cancer prevention.

Goldie et al.[13] using modelling, and assuming coverage of 70% of girls aged 9–12 years, suggested that vaccinating against types 16 and 18 will reduce the lifetime risk of cervical cancer by 43%. In addition, a combined approach of vaccinating young girls and screening women over the age of 30 years, at 70% coverage for both, will provide an estimated 53–70% reduction in the lifetime risk of cervical cancer. At coverage rates of 100% the expected cancer reduction with vaccination alone reaches 61%, but with the combination of vaccination and screening older women, the reduction is approximately 75%.

From a developing country point of view introducing the HPV vaccine into public health poses many challenges. The most obvious is cost and the present price of both vaccines is unaffordable. However, cost is only one aspect. Firstly, no developing countries have established pubescent/adolescent health platforms or school health systems from which to vaccinate young girls (and possibly boys). This infrastructure will have to be created de novo and for this to happen, a great deal of political will will need to be generated. Unfortunately no studies have been done on infants, so neither vaccine will be able to be integrated into the Extended Programme for Immunisation (EPI) that is found in many developing countries and which is believed to save 3 million young lives per year.

Besides the need to create a new infrastructure, the vaccine requires a cold chain, thus a reliable source of electricity, which is notoriously difficult in many developing countries, particularly in Africa. The need for 3 injections and therefore follow-up poses its own challenges as does the necessity for intra-muscular injection (skills, medical waste disposal). Furthermore, one is injecting a young girl to prevent a disease that will only manifest in 30 or so years time. Developing a national strategy will require those familiar with vaccination (pediatricians, public health officials) to communicate with those who work in the cancer world (traditionally two worlds that never intersect). However, developing a pubescent or adolescent health platform may be highly desirable. Such a platform would be a unique opportunity to offer parallel services to young people e.g. booster vaccination against Hepatitis B, tetanus, possibly HIV in the future, deworming, nutritional assessment, education around drug, tobacco and alcohol use, pregnancy prevention and sex and sexuality in general.

In summary, implementing the HPV vaccine involves a great deal more than cost and getting the needle in the arm.

Secondary Prevention of Cervical Cancer

It is beyond the scope of this article to critically evaluate strategies for secondary prevention of cervical cancer. Suffice to say, that countries that have implemented mass, organised, cytology-based screening programmes have dramatically reduced the incidence of and mortality from cervical cancer[14]. However, establishing and sustaining organised cytology-based screening programmes has proven to be too complex and too expensive for the majority of developing countries. This has prompted researchers to evaluate alternative protocols and strategies for the prevention of cervical

cancer, particularly Visual Inspection with Acetic Acid (VIA) and HPV DNA testing. For a comprehensive review of these alternatives strategies see reference 15.

CANCER OF THE PENIS

Worldwide, SCC of the penis is rare, accounting for less than 0.5% of cancers in men. In developed countries the ASIR range from 0.3 – 1/100 000. However, higher incidence rates are observed in India, parts of Southeast Asia, Latin America (Brazil and Columbia) and Africa (Uganda), where the incidence can reach 4/100 000. In Europe about 4000 cases are diagnosed per year, accounting for less than 0.5% of all cancers[16]. Penile cancer generally occurs late in life, with a mean diagnosis at age 60 years.

The natural history of penile cancer most likely follows a long period of pre-neoplastic change ultimately progressing to invasive cancer. Risk factors include smoking, phimosis and poor hygiene. Circumcision however, reduces the risk of penile cancer three-fold[17]. While being uncircumcised is considered a relatively important risk factor for penile cancer, infection with HPV is probably more important.

In a study of 83 patients with primary invasive penile SCC treated in the Netherlands between 1969 and 2000, Heideman et al.[18] found HPV DNA in 55% of cases. HPV 16 was the predominant type being found in 52% of those cases positive for HPV DNA.

A systematic review of HPV prevalence in invasive penile cancer was performed by Backes et al.[19]. From a total of 30 studies, 1 266 cases of SCC of the penis were reported on. All cases were typed using PCR. HPV prevalence was 47.9%, ranging from 22.4% in verrucous SCC to 66.3% for basaloid/warty subtypes. There was some geographic variation ranging from 39.7% in South America to 59.3% in Asia. Analyses of type-specific HPV prevalence were limited to 27 studies of SCC (n = 1 185). Among these studies 22 HPV types were detected, with the three most common types being HPV 16 (30.8%), HPV 6 (6.7%) and HPV 18 (6.6%). Combined prevalence of HPV 16 and 18 (the types found in the HPV vaccines) was 36.7%, suggesting that vaccination may also prevent penile cancer in over a third of cases.

OTHER CANCERS

HPV DNA is found in a high proportion of basaloid and warty types of vulval cancer (> 55%) which occur in younger women than keratinising cancers and are associated with classical risk factors for the acquisition of HPV. In one study 42% of 46 women with vulval cancer were HPV DNA positive, and 93% of those positive were high risk types[19]. Among HPV DNA positive vulval cancers the predominant type is HPV 16[20]. Vaginal cancer, which has a similar epidemiological profile to cervical cancer, is a rare diagnosis, accounting for less than 2% of all gynecological cancers. HPV DNA and HPV antibodies are identified in up to 91% of invasive vaginal cancers and over 80% of vaginal intraepithelial lesions. Similar to cervical cancer HPV 16 is the commonest HPV type identified[21,22]. Studies using PCR for HPV detection in anal cancer indicate that the prevalence of HPV DNA is over 80%, with HPV 16 being the most common type in SCC and HPV 18 in a much smaller percentage[23]. Head and neck cancers, i.e. SCC arising in the upper aerodigestive tract (oral cavity, oropharynx, hypopharynx and larynx) are mostly associated with alcohol and tobacco exposure, however in around 25.9% of cases, HPV DNA can be detected, with HPV 16 being the most common type identified (23.5% for cancers of the oral cavity and 35.6% for oro-pharyngeal cancers)[24-25].

BENIGN DISEASE: GENITAL WARTS

While genital warts in both men and women are benign, they are associated with significant morbidity, in terms of symptoms and psychosexual stresses. More than 90% of genital warts are related to HPV types 6 and 11. In 20 – 50% of cases of genital warts, there may be co-infection with high-risk

types of HPV. In a sample survey of 11 161 men and women in the United Kingdom, aged 16 – 44 years, 3.6% of men and 4.1% of women reported ever being diagnosed with genital warts[26]. In a population-based cross-sectional study of 69 147 women aged 18 – 45 years from Denmark, Iceland, Norway and Sweden, information on genital warts and lifestyle habits was collected using a questionnaire[27]. Overall 10.9% (n = 7351) of those interviewed reported ever having had clinically diagnosed genital warts, and 912 (1.3%) had experienced genital warts in the past 12 months.

In conclusion, Parkin[28] estimated in 2002 that of the nearly 6 million cancers in the developing world diagnosed in the cervix, penis, vulva, vagina, anus, mouth, oropharynx nearly 450 000 were attributable to infection with HPV. In developed countries, of just over 5 million cancers of the same organs, 111 500 were attributable to HPV infection.

While cancer of the cervix is the most common cancer with a strong etiological relationship to infection with high risk types of HPV, other cancers have a not insignificant relationship to HPV infection, and in the majority of cases with type HPV 16. These data suggest that preventing infection with HPV 16, in particular, as well as HPV 18 is likely to be associated with a significant reduction in disease burden, globally. Prevention of genital warts through vaccination against types 6 and 11 will contribute significantly to this reduction in the global disease burden attributable to HPV.

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