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Human papillomavirus infection and the development of cervical cancer and related genital neoplasias

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KEYWORDS
Cervical cancer;
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Human papillomavirus;
Genital warts;
Prevalence;
Screening;
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Summary
Background: The human papillomaviruses (HPV) are simple, nonenveloped, double-stranded DNA viruses, which are responsible for an enormous global burden of genital disease. HPV is associated with 500,000 new cases of cervical cancer and 250,000 cervical cancer deaths worldwide each year. Oncogenic HPV types 16 and 18 are responsible for a majority of cervical cancers and can also cause low- and high-grade cervical lesions (CIN 1, 2, 3) as well as high-grade vulvar or vaginal intraepithelial neoplasia (VIN or VaIN 2/3). Nononcogenic types HPV 6 and 11 also contribute to the overall burden of HPV disease, giving rise to CIN 1, anogenital warts, cutaneous lesions, and respiratory papillomatosis.
Perspectives: A substantial body of clinical evidence demonstrates the effectiveness of cytological screening in preventing cervical cancer, but these techniques have not eradicated the disease and are not widely available in most developing countries. Furthermore, evaluation and management of HPV-associated cytologic abnormalities is costly, drains health care resources, and increases the risk for adverse pregnancy outcome.
Conclusions: Targeting cervical cancer through universal immunization with a quadrivalent HPV 6, 11, 16, 18 vaccine may herald the beginning of the end of this deadly disease and substantially reduce the overall global burden of HPV-related genital diseases.

Introduction

Throughout the world, human papillomavirus (HPV)-associated disease is an immense public health burden. At least 50% of men and women will acquire genital HPV infection during their lifetime.[1] HPV is associated not only with 500,000 new cases of cervical cancer and 250,000 associated cervical cancer deaths worldwide each year[2] but also causes vulvar, vaginal, anal, and penile cancers[3–7] as well as cervical, vulvar/vaginal precancerous lesions, genital warts, and respiratory papillomatosis.[8–14] Most individuals are not aware that they are infected with HPV because of its subclinical or asymptomatic presentation, and, thus, the virus can be spread easily and unknowingly during sexual foreplay or sexual intercourse.[12,15,16]

The purpose of this article is to review the structure, types, and epidemiology of HPV, and provide some insight into the global burden of HPV-related disease, especially

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cervical cancer, which continues to be a major threat to women's health despite the introduction of Papanicolau (Pap) smear screening techniques more than 50 years ago.

Structure and types of HPV

Papillomaviruses, including human papilloma virus (HPV), are nonenveloped, double-stranded DNA viruses. The genome of HPV is small in size (8 kb) and encodes 8 genes. These genes code for 6 nonstructural early proteins (E1, E2, E4, E5, E6, E7) and 2 structural or late proteins (L1, L2). Of the more than 100 HPV types characterized, roughly 40 types infect the human genital tract where they can induce a wide range of clinical manifestations, including cervical, vaginal, and vulvar intraepithelial neoplasias (CIN, VaIN, and VIN, respectively), and cancer of the cervix, vagina, and vulva in women, as well as genital warts (condylomata acuminata) in women and men.[17-20]

Genital HPVs are categorized into high-risk and low-risk types defined by the strength of epidemiologic evidence linking them to development of cervical cancer. Analysis of pooled case-control data of women in 9 countries with confirmed squamous-cell cervical cancer identified 15 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) as high risk — that is, they were strongly related to precancer and cancer of the anogenital region. An additional 3 types were identified as probably high risk (26, 53, 66) and 12 types (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108) as lower risk for cervical cancer.[21]

Considerable differences exist in HPV types detected in healthy women from different geographic areas, as shown by a pooled analysis of HPV prevalence surveys in women without cervical cytological abnormalities in 11 countries (Nigeria, India, Vietnam, Thailand, Korea, Colombia, Argentina, Chile, the Netherlands, Italy, and Spain).[22] This heterogeneity, whilst less than that observed for many viral and bacterial diseases, may have important clinical ramifications with respect to employing screening tests for specific virus types and the potential impact of vaccines on the incidence of HPV infection. However, strikingly, when considering women with clinical lesions, the more advanced the lesion the less heterogeneous is the type distribution across countries.[23-25] Worldwide HPV 16 and 18 as a major cause of cervical cancer is remarkably consistent, being found in 64–79% of cases of cervical cancer, depending on the region.

Risk of acquiring HPV infection

HPV infection is frequently acquired in adolescents and young adults within months after first sexual intercourse.[8,26-29] Up to 80% of women will likely acquire genital HPV infection by the age of 50.[1,30]

A strikingly high HPV DNA prevalence rate has recently been demonstrated among young women in Helsinki, Finland. One third of 1st year university students attending a health clinic or visiting a general practitioner for health examination tested positive for any HPV in vaginal or cervical samples.[31] The cumulative incidence of first-time HPV infection in a cohort of female university students in Washington State was also shown to be high.[32] Of the women who initiated sexual activity during the study, first-time HPV infection occurred in 32.3% after 24 months (Figure 1). Additional evidence of rapid acquisition of HPV comes from a study of UK adolescents (15–19 years of age, who had had only one sexual partner).[29] This study revealed that the median time from sexual debut to first detection of HPV was only three months and the 3-year cumulative risk of acquiring cervical HPV was 46% (Figure 1).

Although the risk of HPV infection remains high throughout a woman's life, the highest risk is in adolescents between the ages of 15–19 years. A study of HPV-negative Colombian women 15–85 years of age with normal cervical cytology at baseline clearly showed that, for any HPV infection, the highest 5-year cumulative risk occurred among women 15–19 years of age (42.5%) and thereafter decreased with age, with women 45 years of age and older having the lowest risk (12.4%).[33]

A majority of episodes of a type-specific HPV infection spontaneously resolve within 2 years but many young

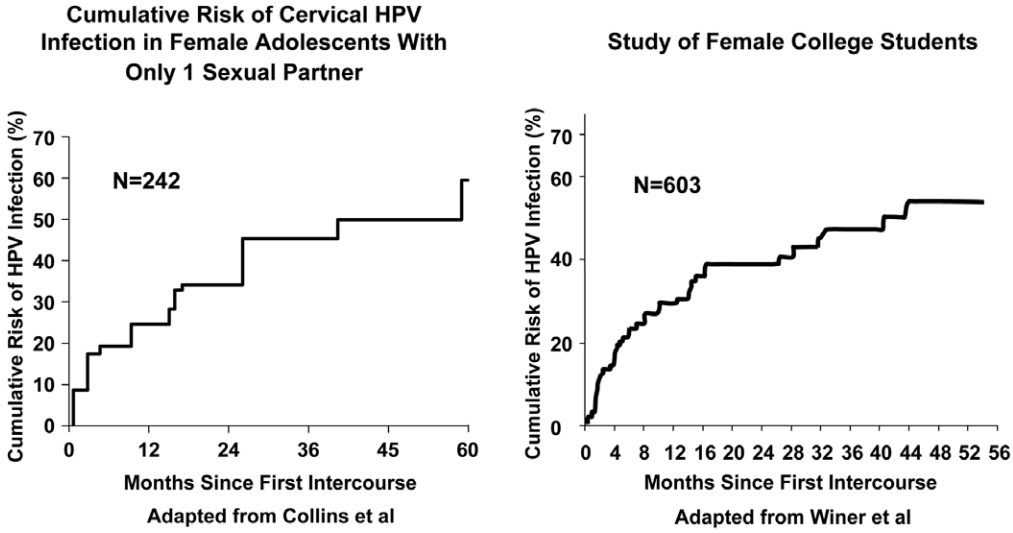

Figure 1 Studies in the UK and US show rapid acquisition of HPV in young women after first intercourse. Reproduced with permission.[29,32]

women may become infected with a new HPV type.[34] In a cohort of adolescent women followed closely over a 2.2-year period, the median duration of persistence of a specific HPV type was 168 days, but high risk oncogenic HPV types were more persistent than low risk types (P = 0.034).[35] Persistence of infection is an important clinical consideration because this is the major risk factor for malignant transformation of cervical cells.

HPV transmission

HPV transmission almost exclusively occurs following skin-to-skin contact with an infected partner. Sexual intercourse is not strictly necessary and the virus can also be transmitted during sexual foreplay including fingers.[15] To date, there is little or no evidence to suggest that HPV can be transmitted by nonsexual routes (that is, environmental transmission). HPV is exclusively an intraepithelial pathogen and is unable to propagate in cell culture. HPV can only replicate in stratified squamous epithelium and, to do so, exploits the natural differentiation program of basal keratinocytes. As a result of microabrasions or tears that can occur during sexual activity, HPV penetrates and infects the basal keratinocytes of the epithelium, where it may persist in a latent state. As the basal cells differentiate and mature, the HPV genome is replicated episomally with the aid of two HPV nonstructural proteins (E1 and E2). Other nonstructural proteins (E6 and E7) are then expressed, which delay the natural maturation of epithelial cells in order to exploit the host cell's DNA machinery to synthesize the structural proteins (L1 and L2) needed for viral assembly. As a result of E6 and E7 disrupting cell division, infected epithelial cells out grow noninfected cells and give rise to dysplasia, warts, or tumors. The entire process eventually results in the release of new virus particles (virus-laden squames or koilocytes) to the epithelial surface. The shedding of koilocytes serves as the vector of HPV transmission, with each koilocyte containing approximately 50–100 virions.

The normal cervix may be particularly vulnerable to HPV infection during periods of squamous metaplasia (e.g., during early adolescence and first pregnancy) when large regions of rapidly proliferating cells occur.[15,36] Infection of the cervix with high-risk HPV types (e.g., 16 and 18) resolves spontaneously in many patients probably through the actions of the immune system. However, in some patients who are persistently infected by the virus, the HPV genome can become integrated into the DNA of the host cells, leading to precancerous and subsequent cancerous changes resulting from interference with the normal control of the cell growth cycle.[36]

World burden of HPV-related disease

Genital HPV infections are associated with a wide spectrum of disease. Most patients with cervical HPV infection, approximately 300 million cases worldwide annually,[9] are typically never seen in a gynecology practice because the HPV infections do not lead to any detectable cytologic abnormalities and clear spontaneously or because there is no access to care. An important subset of these patients subsequently progress to low- and high-grade cervical dysplasia (30 million and 10 million cases, respectively), and eventually cervical cancer (0.5 million cases).[9] After breast cancer, cervical cancer is the most frequent cancer in women 15–44 years of age in Europe.[37] HPV 16 and 18 are responsible for a majority of cervical cancers worldwide and can also give rise to low- and high-grade cervical lesions (CIN 1, 2, 3).[21]

In addition to cervical cancer, high-risk HPV is also associated with approximately 50% or more of vaginal, vulvar, and penile carcinomas; ~85% of anal carcinomas; and 10% of cancers of the larynx and aerodigestive tract (Figure 2).[9,38–40] In addition, approximately 20% of oropharyngeal cancers contain HPV DNA.[40] Many of these cancers are preceded by HPV-associated dysplastic lesions, including vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VaIN), penile intraepithelial neoplasia (PIN), anal intraepithelial neoplasia (AIN), or perianal intraepithelial neoplasia (PAIN).

The rate of VIN has been increasing worldwide and in the United States, particularly in younger women, a trend

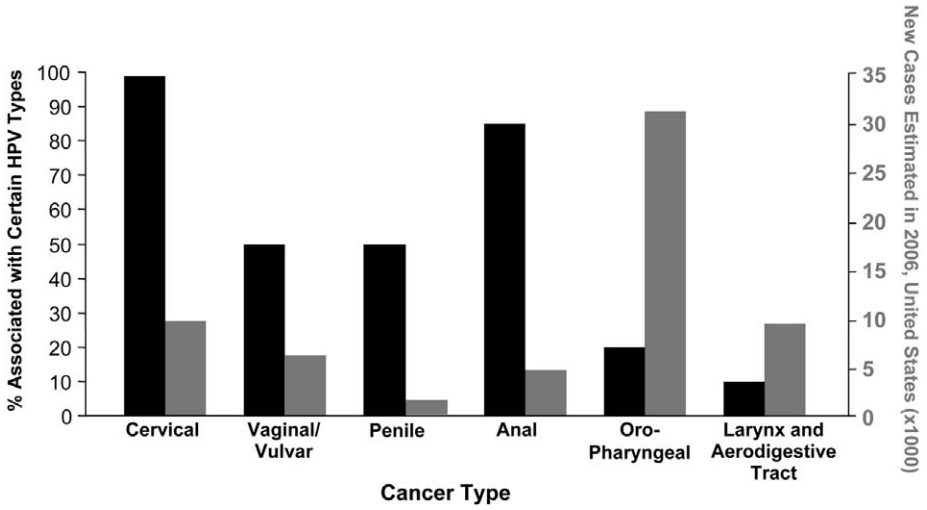

Figure 2 High-risk types of HPV have been identified in a wide range of malignancies.

Table 1 Despite well established screening programs in many European countries, cervical cancer continues to occur

Country	Recommendation		% Regularly screened	Cervical cancer mortality/100,000	Cervical cancer incidence/100,000
	Age range (yrs)	Interval (yrs)			
Finland	30–60	5	93	3.0	6.2
England	25–64	3–5	83	5.1	10.5
Sweden	23–60	3	83	5.6	10.9
Belgium	25–64	3	78	6.2	12.8
The Netherlands	30–60	5	77	3.8	9.4
Denmark	23–59	3	75	8.6	16.3
France	25–65	3	69	5.4	13.6
Italy	25–64	3	53–74	4.0	11.6
Germany	20–85	1	50	7.1	14.7
Spain	25–65	3	27	3.6	10.3
US	21–30	1	79	2.5	8.7
(for comparison)	>30	2–3			

Data obtained from Anttila A, Ronco G, Clifford G, et al. *Br J Cancer.* 2004;91:935–941[61]; van Ballegooijen M, van den Akker-van Marle E, Patnick J, et al. *Eur J Cancer.* 2000;36:2177–2188[62]; Ferlay J, Bray F, Pisani P, Parkin DM. Lyon, France: IARC Press; 2004[37]; US Department of Health and Human Services. Healthy People 2010. Vol. 1–2, 2nd edition. Washington, DC: US Government Printing Office: 2000. (Level III)[63]; Clinical Management Guidelines for Obstetrician-Gynecologists. ACOG Practice Bulletin 2003;102:417–427[64]; Clinical US Cancer Statistics Working Group. United States Cancer Statistics: 2002 Incidence and Mortality. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute[65].

that appears to be associated with HPV infection.[41,42] For example, in the United States over the period 1973 to 1987, the rate of VIN 3 doubled (from 1.1 to 2.1 per 100,000 women-years), exceeding the rate of invasive vulvar cancer.[42] HPV 16 appears to be the dominant HPV type associated with high-grade VIN, followed by HPV 18.[43,44]

It is important to note that a clinically important segment of the overall burden of HPV disease is associated with nononcogenic HPV 6 and 11. These two HPV types are not only associated with low grade cervical lesions and anogenital warts but also cutaneous lesions, and respiratory papillomatosis.[45,46] In addition, the clinical consequences of HPV 6 and 11 infections tend to become manifest more rapidly compared with high-risk HPV types – for example, incident HPV 6 and 11 invections can give rise to genital warts over a time frame considerably shorter than the time from first HPV infection to high-grade CIN.[47] Genital warts are almost exclusively caused by HPV 6 and 11,[48] are extremely contagious,[49]and result in a high level of emotional distress and anxiety.[12,50–52] Available chemical, immune enhancing, or surgical ablative treatments for genital warts are often followed by recurrences and are costly and painful.[53]

Cervical cancer — continued occurrence despite screening programs

Cellular atypia of the cervix can only be accurately detected by cytopathological analysis of the cervical epithelium. The gold standard for identifying precancerous cervical dysplasia is the Pap smear, introduced over 50 years ago. This cheap, noninvasive test is the foundation for effective early detection and evidenced-based therapeutic interventions.

Although wide variation exists in screening policies among European countries,[54] there is sound clinical evidence demonstrating the effectiveness of cytological screening in preventing cervical cancer. In Finland, cervical cancer incidence and mortality rates (tracked by the Finnish Cancer Registry since 1953) abruptly declined after 1962 following the introduction of a cervical cancer screening program. However, in Finland, as in many other European countries, cervical cancer has not been eradicated and continues to represent a considerable public health challenge despite established screening programs (Table 1).

It is important to appreciate that for every case of invasive cancer detected by cytological screening, there are many more women with precancerous lesions or atypical squamous cells of undetermined significance (ASC-US).[55] These cases require careful long-term follow-up, multiple clinic visits, often evaluation by colposcopy and biopsy, and an adequate infrastructure to process and analyze cervical specimens.[55,56] Thus, while evaluation and management of HPV-associated cytologic abnormalities has markedly reduced cervical cancer rates, it is extremely costly, placing an enormous burden on the healthcare system. In the United States, the direct HPV-attributable medical costs of evaluating abnormal cervical cytology and subsequent treatment of related neoplasias has been estimated to be $3.4 billion annually among women of all ages.[57] Furthermore, it should also be pointed out that one of the most frequent reasons for medical malpractice litigation in the US is false negative Pap smears in women with HPV-associated precancerous lesions.[55]

Treatment of CIN is also not without deleterious long-term consequences for some patients, increasing both risk of cervical and other cancers.[58] A recent Finnish study assessing the 20-year risk of cervical and other cancers in

women treated for CIN showed that surgical treatment of CIN was associated with an increase in the standardized incidence ratio (ratio of observed to expected number of cases) of cancer of the cervix (2.8, 95% confidence interval [CI] 1.7–4.2), vulva (4.1 95% CI 1.5–8.9), vagina (12.0, 95% CI 3.9–28), and anus (5.7, 95% CI 1.2–17).[58]

A recent meta-analysis of 27 studies indicates that treatment of young women with mild cervical abnormalities using excisional procedures may increase the risk of subsequent adverse pregnancy outcome.[59] Surgical removal of intraepithelial lesion by techniques such as CO_2 laser excision, large loop excision of the transformation zone (LLETZ), loop electrosurgical excision procedure (LEEP), or cold-knife conization were all associated with varying negative effects on preterm delivery, low birthweight, need for caesarean section, and premature rupture of the membranes. As a result of these findings, the authors recommended caution in the treatment of young women with mild cervical abnormalities.

Conclusions

HPV infections are highly prevalent, especially in adolescent women between the ages of 15–19 years, resulting in an enormous burden of disease worldwide. Although many HPV infections clear spontaneously without any intervention, persistent infection with oncogenic HPV types increases the risk for a wide range of genital neoplasias, including cervical, vulvar, vaginal, and penile cancers. In addition, nononcogenic HPV 6 and 11 types contribute to the overall burden of HPV disease, giving rise to anogenital warts, low-grade Pap smear atypias, and respiratory papillomatosis (rare). Although an effective tool in reducing the incidence of cervical cancer, cytological screening techniques have not eradicated this disease. Importantly, cervical screening programs are not available in developing countries where more than 80% of cervical cancer cases occur.[60] Furthermore, the evaluation and management of HPV-associated cytologic abnormalities is costly, drains health care resources, and increases the risk for adverse pregnancy outcome.

A prophylactic quadrivalent HPV vaccine is now available that induces the formation of virus-neutralizing antibodies, preventing HPV infection with the virus types contained in the vaccine. Universal immunization with a quadrivalent HPV vaccine can be expected to have a substantial impact on the overall burden of HPV-related genital diseases and may actually herald the beginning of the end of cervical cancer.

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Conflict of Interest statement

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