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REVIEW

Risk factors for and prevention of human papillomaviruses (HPV), genital warts and cervical cancer

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Summary Genital HPV infection is associated with development of cervical cancer, cervical neoplasia, anogenital warts, and other anogenital cancers. A number of reviews have primarily addressed the role of HPV infection in cervical carcinogenesis, and differences in human papillomavirus (HPV) subtypes found in cervical cancer cases by histology and geographical region. This review provides an informative summary of the broad body of literature on the burden of HPV, the risk factors for HPV infection, genital warts and cervical cancer, and preventive measures against these conditions in females. Studies have identified the main risk factors for genital HPV infection in females as follows: acquisition of new male partners; an increasing number of lifetime sexual partners both in females and their male partners; and having non-monogamous male partners. Cervical cancer screening and HPV vaccination are the primary measures currently recommended to prevent cervical cancer. There is also an ongoing debate and conflicting findings on whether male circumcision and condom use protect against HPV infection and subsequent development of HPV-related illnesses in females.

For over two decades, a substantial amount of research has been undertaken on the etiology and risk factors for cervical cancer and genital warts, specifically with regard to the role of human papillomaviruses (HPV). More recently, the focus has shifted to measures to prevent HPV infections as well as cervical cancer screening for early diagnosis and

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treatment of cervical cancer. Despite progress made to date on prevention of HPV infection in both females and males, there are continuing controversies and debates regarding the long-term efficacy of HPV vaccines and whether condom use and male circumcision offer protective effects. The purpose of this paper is to review and summarize the current evidence regarding risk factors for and prevention of HPV infection, genital warts and cervical cancer.

Human papillomaviruses (HPV)

HPV infection

Papillomaviruses are double-stranded deoxyribonucleic acid (DNA) viruses that are small, non-enveloped and icosahedral with a diameter of 52—55 nm.[1,2] They are also epitheliotropic, which means that they generate productive infections merely within the stratified epithelia of the skin, oral cavity and anogenital tract. Infection of basal epithelial cells initiates the viral life cycle, which is linked to differentiation of the infected epithelial cells.[3]

Of more than 100 HPV types that have been differentiated molecularly, approximately 40 types are known to infect the genital tract.[4] HPV infections are the most common sexually transmitted infections globally. Genital HPV infection is associated with development of cervical cancer, cervical neoplasia, anogenital warts, and other anogenital cancers.[3] However, cervical infections with HPV are often asymptomatic and clear within one to two years of infection through the hosts' cell-mediated immunity.[5] Worldwide, the prevalence of HPV infections among women with normal cytology is about 10%.[6—8] However, in all world regions, there are age disparities in HPV prevalence whereby women under the age of 35 years have the highest HPV prevalence.[8] For instance, among college women participating in a longitudinal study in the U.S., HPV prevalence among females with normal cytology was 24.4%.[9]

HPV-16 and HPV-18 were classified as human carcinogens in 1995 by the International Agency for Research on Cancer (IARC).[10] Data pooled from 11 case-control studies resulted in the classification of 15 HPV types as *high-risk* (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), three HPV types as *probable high-risk* types (26, 53, and 66), and 12 HPV types as *low-risk* (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108).[11] High-risk HPV types are considered to be carcinogenic and are often associated with invasive cervical cancer (ICC). On the other hand, low-risk HPV types are mainly associated with genital warts.[12] In women with normal cytology who are infected with high-risk HPV types, HPV-16 infections have a significantly lower 18-month clearance rate than other high-risk HPV types. Furthermore, women with HPV-16 infections that persist are more likely to develop cervical intraepithelial neoplasia (CIN) grade 3 (CIN3) or cervical cancer than women who have persistent infections with other high-risk HPVs.[13]

Prevalence of HPV DNA in ICC cases — regardless of HPV type — is homogenous across geographic regions, ranging from 75% to 100%.[14] A meta-analysis of HPV prevalence in over 10,000 ICC cases from 85 studies found no significant geographical differences. Adjusting for histological type, geographic region, type of HPV DNA specimen, and polymerase chain reaction (PCR) primers used in HPV detection, HPV prevalence was reported as follows: 87.7% in South and Central America; 88.1% in North America and Australia; 86.7% in Europe; 79.3% in Asia; and 86.5% in Africa.[15]

Conversely, the prevalence of HPV among women with normal cytology is lower in developed countries (10.0%) compared to less developed regions (15.5%). Worldwide, HPV-16 followed by HPV-18 are the most prevalent HPV types in women with normal cytology. By geographic region however, HPV-18 is the second most common HPV type in Europe, Central America and South America, but ranks third in Africa and fourth in Asia and North America. HPV-52 is the second most prevalent HPV type in Africa and Asia, while HPV-53 ranks second in North America.[8]

Burden of HPV

Harald zur Hausen, a German virologist, won the 2008 Nobel Prize in Physiology or Medicine for establishing the link between oncogenic genital HPV and cervical cancer in the late 1970s to early 1980s.[16—18] HPV is a necessary cause of cervical cancer. In a multi-national study using data from 22 countries, HPV DNA was detected in 93% of biopsy specimens from over 900 sequential ICC cases.[14] Further analysis of 7% of the specimens that initially tested negative for HPV DNA increased the prevalence of HPV in ICC cases to 99.7%, leading to the conclusion that HPV-negative cervical cancers are very uncommon.[19]

An estimated 70% of invasive cervical cancers have been attributed to HPV-16 (55%) and HPV-18 (15%) globally. HPV-16 and HPV-18 are also responsible for approximately 50% of CIN3.[20] In young women with incident HPV-16 or HPV-18 infections, 20% and 6.7% develop CIN grade 2 (CIN2) and CIN3, respectively, within 36 months of infection.[21]

Of more than 35 HPV types, five types (HPVs 16, 18, 45, 31 and 33) account for 80% and 94% of the distribution in squamous cell carcinomas (SCC) and adenocarcinomas (ADC) of the cervix, respectively.[22] Moreover, in a pooled analysis of 11 case-control studies, 95% of SCCs positive for HPV DNA were due to HPV types 16, 18, 45, 31, 33, 52, 58, and 35.[11] The overall HPV prevalence does not vary between SCC, ADC, and adenosquamous carcinomas (ADSC) of the cervix.[15] In an IARC multi-center case control study, 94.6% of SCC cases and 90.9% of ADC/ADSC cases were positive for HPV DNA.[23] However, there is variation in HPV prevalence by HPV type in these carcinomas. The relationship between HPV type and tumor histology has shown that 68% of viral types found in SCC are accounted for by HPV-16 and related viruses (HPV types 31, 33, 35, 52, and 58). For both ADC and ADSC, 71% of viral types found in these tumors are accounted for by HPV-18 and related viruses (HPV types 39, 45, 59, and 68).[14] A meta-analysis of over 10,000 ICC cases from all continents found HPV-16 prevalence to be significantly higher in SCC (55.2%) than ADC and ADSC combined (31.3%). In contrast, HPV-18 prevalence was significantly lower in SCC (12.3%) than ADC and ADSC combined (37.7%).[15]

HPV is also associated with vaginal and other anogenital cancers. It has been found in a large proportion of vaginal cancers (64%—91%), severe vaginal intraepithelial neoplasia (VAIN-3) lesions (82%—100%), and anal cancers (88%—94%).