Risk Factors Affecting HPV Infection, Persistence and Lesion Progression in Women and Men

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Abstract

Human papilloma virus (HPV) is a common sexually transmitted infection, which affects three-quarters of sexually active people at some period of their life. HPV-infected persons often have no symptoms, but they are still infected and can transmit the virus to others. Approximately 90% HPV infection cases pass on its own during a couple years without any intervention. Not all HPV types are dangerous and lead to virus persistence or cell changes. Estimating the risk to cause cervical cancer, HPV types are classified into low-risk (6, 11, 34, 40, 42, 43, 44, et al.), high-risk (31, 33, 35, 39, 45, et al.) and particularly high-risk (16, 18) HPV. It is important that high-risk HPV (especially, 16 and 18) enters basic cells which are into skin or mucous membrane, the virus begins to make some oncoproteins which act cooperatively in promoting cervical carcinogenesis. All sexually active women are at risk of HPV infection and subsequent development of a cervical abnormality. The most important factor in the progression of cervical cancer is HPV infection and the type of HPV. Other infection persistence influencing factors (such as unsafe sexual behavior, mode of infection pathway, smoking, alcohol, long-term use of oral contraceptives, immunosuppression and sexually transmitted infections) will only help to increase it.

ABBREVIATIONS

HPV: Human Papillomavirus; CIR: Cumulative Incidence Rate; STI: Sexually Transmitted Infections; OCs: Oral Contraceptives

INTRODUCTION

Human papilloma virus (HPV) is a common sexually transmitted infection, which affects three-quarters of sexually active people at some period of their life. Based on 2006 data, 630 million people worldwide have been infected with HPV [1]. Detailed meta-analysis (2010), with data extracted from 194 studies and based on testing over one million women, indicates that the global prevalence of HPV infection is around 11–12% [2].

However, not all HPV types are dangerous and lead to virus persistence or cell changes. Estimating the risk to cause cervical cancer, HPV types are classified into low-risk (6, 11, 34, 40, 42, 43, 44, et al.), high-risk (31, 33, 35, 39, 45, et al.) and particularly high-risk (16, 18) HPV.

HPV-infected persons often have no symptoms, but they are still infected and can transmit the virus to others. At once people can be infected not one but several types of HPV. Approximately 90% HPV infection cases pass on its own during a couple years without any intervention [2]. HPV infections may be less likely to persist in men than in women. It is known that, in men, the median time to clearance of any HPV infection is 5.9 months, with 75% of infections clearing within 12 months [3]. However, sometimes HPV infection remains in the body and persist which can cause cervical cancer in women as well as other anogenital cancers or oropharyngeal cancer, and genital warts in both genders.

The pathways of HPV infection are sexual and non-intercourse: contact or perinatal. Anyone who has or has had sexual intercourse (vaginal, oral or anal) can or could get HPV. This infection is very common and it is suggested that sexually active people at least once in their life is faced with HPV. Even those who have had only one sexual partner could also get HPV.

HPV infection makes some histological changes which depend on the type of virus. When high-risk HPV (especially, 16 and 18) enters basic cells which are into skin or mucous membrane, the virus begins to make some oncoproteins (E6 and E7) [4]. These oncoproteins act cooperatively in promoting cervical carcinogenesis, such as interfering with cell functions that normally prevent excessive growth (tumor suppressors p53), helping the cell to grow in an uncontrolled manner and to avoid cell death [5].

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- Risk

Nowadays, risk factors affecting HPV infection, persistence and lesion development are not well understood. Many studies have investigated the influence of behavioral factors on acquisition and persistence of infection and development of lesions, also the influence of immunosuppression and other sexually transmitted infections (STI) [6,7].

**CO-FACTORS, THAT INCREASE THE HPV RISK**

**Unsafe sexual behavior**

More than 40 % young women are infected with HPV during the first 2 years after the start of sexual activity. Especially high risk of infection is for adolescents and younger than 25 years sexually active women [1]. The main reason why young women are more vulnerable to HPV infection is biological. Anovulatory cycles lead to inadequate production of cervical mucus (protective barrier against infectious agents). Also cervix physiological immaturity (during puberty the cervix undergoes cellular changes at the transformation zone that are known as ectopy) leads to HPV infection by rapid rate of metaplastic changes and the incomplete immune responses. During ectopy, the cervical cells may not only be more susceptible to HPV infection, but they may also be more prone to persistent HPV infection and lasting damage from an infection [8-10]. Ribeiro et al. [11] and Baudu et al. [12], found a significant association among women who had their first sexual intercourse prior to 16 years of age and HPV infection. Sexual life with lots of different partners also increases chances of coming into contact with a person who is carrying the HPV. Some studies showed that women, who had during their life two or more partners, have twice higher prevalence of HPV than those who had only one partner [6,13].

The most consistently reported risk factor for HPV infection in men is a greater lifetime number of female or male sex partners. Men, who had more than 10 partners during their lifetime, have twice bigger chance to get infected by HPV. Also there are positive associations between HPV detection and sexual frequency, condom use and men circumcision. It is known that lower prevalence of HPV infection is for those who always used condoms because of less skin-to-skin contact.

**Mode of infection pathway**

The risk of getting infected by HPV also depends on virus pathways. HPV is transmitted by skin-to-skin contact and requires access to basal cells through micro cuts, abrasions or small tears in the squamous or mucosal epithelium [14]. Other STI (genital warts, herpes simplex, C. Trachomatis) cause inflammation and breaks in the epithelium barrier, allowing HPV direct access to basic epithelial cells [15,16]. Genital HPV infections are contracted through sexual intercourse, anal sex and other skin-to-skin contact in the genital region. Some HPV infections that result in oral or upper respiratory lesions are contracted through oral sex. It is also spread through both heterosexual and homosexual relationship [17,18]. Some men are more likely to develop HPV-related diseases than others: gay and bisexual men are about 17 times more likely to develop anal cancer than men who only have sex with women.

**Circumcision**

A lot of studies have been done to detect the influence of circumcision. Circumcised men are less likely to get penile and prostate cancer. The foreskin is simply more sensitive to HIV infection than the skin on your shaft, according to the CDC (Centers for Disease Control and Prevention). Another possible explanation: The foreskin is susceptible to tearing during the intercourse, which would give viruses an easy pathway into your body. Or it could be that the folds in foreskin provide an environment for viruses and bacteria to thrive. HPV infection in men (HIM) study showed that time to clearance of any HPV infection was significantly longer among circumcised men than uncircumcised men [19]. However, some researches state that men circumcision was not associated with an overall reduction in the incidence of genital HPV detection in men.

**Smoking**

Several studies showed that cigarette smoking is associated with HPV prevalence [20], incidence [21], and persistence [22]. Women who smoke are about twice as likely as non-smokers to get cervical cancer. The cervical mucus of smokers contains measurable amounts of cigarette constituents and their metabolites [23]. Researchers believe that these substances damage the DNA of cervix cells, increase cell proliferation and may contribute to the development of cervical cancer [22-24]. Smoking was recently identified as a risk factor for HPV detection in men, and it has been reported to be associated not only with virus persistence but also with anal and penile cancer [25]. It is known that smoking also makes the immune system less effective in fighting HPV infections associated with genital area (especially warts) as well as oropharyngeal [26].

**Alcohol**

Alcohol usage is a potent modulator of immune function which can lead to immune deficiency and increased sensitivity to different chronic and infectious diseases. Not only chronic alcohol abuse but also acute and moderate alcohol consumption can adversely affect the immune system. Pathogen response is separated into two phases: the first phase is an inflammatory reaction, which provides protection against the immediate effects of the infection, and the second phase involves the development of immunity to the pathogen. Alcohol consumption can interfere with both phases of the immune response [23,24]. Based on literature data, men and women high intake of alcohol is associated with an increased risk for: having multiple HPV types, which leads to higher cervical/anal lesion and more common genital warts. The study made in Washington reported that four alcoholic drinks/week was associated with doubled risk of genital warts and five or more alcoholic drinks/week revealed a 2,4 times bigger risk [27].

**Long-term use of oral contraceptive**

There is evidence that oral contraceptives (OCs) used for a long time are associated with cervical cancer diagnosis among HPV-positive women [24]. Contraceptive use might affect clearance or persistence of HPV infection, progression or regression of pre-neoplastic and neoplastic lesions [30]. Research suggests that the risk of cervical cancer goes up the longer a woman takes oral contraceptives, but the risk goes back down again after the OCs are stopped. There was no bigger risk of cervical cancer in those who used oral contraceptives for up to 4 years. However, use
of OCs for more than 5 years was significantly associated with cervical cancer [30,31].

The American Cancer Society believes that a woman and her doctor should discuss whether the benefits of using OCs outweigh the potential risks. A woman with multiple sexual partners should use condoms to lower her risk of sexually transmitted illnesses no matter what other form of contraception she uses [24].

Immunosuppression

Human immunodeficiency virus (HIV) damages the immune system and puts women and men at higher risk for HPV infections. HPV is believed to be more dangerous among HIV-positive individuals due to the impact of HIV on cell-mediated immunity, a critical component required for clearance of HPV infection [32]. The immune system is significant in killing cancer cells and slowing their growth and spread. In women with HIV, a cervical pre-cancer might develop into an invasive cancer faster than it normally would [24]. Another group of people at risk of HPV infection are those taking immunosuppressive treatments (chemotherapy, monoclonal/polyclonal antibodies, glucocorticoids et al.) to reduce their immune response, because of being treated for an autoimmune or oncological disease, or who have had an organ transplant. In this case, because of lowered blood cells, especially white cells, human organism can be placed at greater risk of infection.

Sexually transmitted infections (STI)

Based on literature data, C. trachomatis infection for HPV positive women is associated with high-grade cervical intraepithelial contravention or cancer. It is also associated with high-risk HPV types of long-term persistence [33]. This infection prevalence among sexually active adolescent reaches 24-30 % [34]. One case-control research showed that, among oncogenic HPV-infected women, antibodies to C. trachomatis were associated with a twofold increased risk of cervical cancer [34]. HPV infection of the cervix is not believed to be inflammatory. However, during C. trachomatis infection it is secreted higher amounts of cytokines resulting in a severe inflammatory state. The inflammation effect to the C. trachomatis infection may lead to chronic cervical tissue damage indirectly resulting from the production of reactive oxygen species, triggering an inflammatory cascade, decreasing cellular immunity, and promoting angiogenesis [34,35].

Another infection that increases risk of cervical cancer is Herpes simplex virus-2. This virus is among several factors that work in conjunction with HPV in boosting cervical cancer risk. Zhao et al., and other studies contribute to understanding the role of HSV 1 and HSV 2 infection in the etiology of cervical intraepithelial neoplasia and cervical cancer [6,36]. These studies found that HSV-2 DNA and serological positivity showed an increasing trend from cases of cervicitis to cervical intraepithelial neoplasia to squamous cell carcinoma also it was correlated with the risk of precancerous and cervical cancer increased.

Based on ATHENA study results (2012-2015), after 3 years in HPV16 positive women the cumulative incidence rate (CIR) of CIN3+ was 25.2%, CIR 5.4% - was of 12 other HPV genotypes infected women [37,38]. Uijterwaal, et al., made USA-Screen study, which showed that the 5 year CIR for HPV16/18 positive women was 21.1% for CIN2+ and 15.2% for CIN3+ [39].

CONCLUSION

All sexually active women are at risk of HPV infection and subsequent development of a cervical abnormality. The most important factors in the progression of cervical and other cancers are HPV infection and the type of HPV. This infection also can increase a man’s risk of getting genital cancers, such as anal or penile, although these cancers are not common. Mostly HPV cause genital warts in men, just as in women. Other infection persistence influencing factors (such as unsafe sexual behavior, mode of infection pathway, smoking, alcohol, long-term use of oral contraceptives, circumcision, immunosuppression and sexually transmitted infections) will only help to increase it.

REFERENCES


