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Review

Risk Factors for Cervical HPV Infection

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Abstract

Human papillomavirus (HPV) infection is known to cause a subset, although not sufficient, of cervical cancer. In this article, we review current data and synthesize evidence on major risk factors associated with cervical HPV infection. A descriptive analysis of etiology and pathogenesis of the HPV infections is contributed in recognizing all the important determinants risks. A model that categorizes the viral genetic factors, as well as, the role of host genes and environmental factors in the pathogenesis of HPV infection is the only way to identify the biological mechanism of pathogenesis. Awareness of risk factors, are vital to achieving improved outcomes for patients with this increasingly prevalent cervical HPV infection.

Keywords: HPV, HPV cervical infection, cervical cancer, risk factors

INTRODUCTION

The first reports about the HPV virus and the effects of HPV infection have come from antiquity. The first HPV virus was described in 1933 by Shope, who recognized rabbit papillomavirus as the cause of skin papillomatosis (Shope and Hurst, 1933). Later, Rous and his colleagues based on the theory of Shope and Hurst, have shown experimentally that the papillary lesions of rabbits can undergo malignant transformation, leading to the appearance of epithelial carcinomas. Particularly, on 1934, after the transmission of wild-type papillomaviruses to domestic hares, a malignant transformation of papillomas into squamous cell carcinoma tumors was observed, demonstrating experimentally the potential oncogenic effect of the HPV (Rous and Beard, 1933).

The HPV is a small DNA virus with a diameter of 52 - 55 nm. It includes a 8 kb circular double-stranded DNA molecule, with a molecular weight of 5.2 x 106 Daltons, surrounded by histones of cellular origin, forming a chromosome structure. The entire viral complex consists of 72 capsomeres arranged in a pentameric structure that surrounds its genome. The HPV genome is surrounded by a protein coat that promotes the adhesion and integration to the affected cells, as well as genetic material containing all the necessary information about reproduction and viral proliferation. Although the HPV genome demonstrates a common organization among all subtypes of the virus, however, the differences in regulation of expression and function of their genes, affect in various ways their biological response and pathogenicity (Howley and Schlegel, 1988).

According to the risk of oncogenesis, the subtypes of the HPV are distinguished at high and low risk. Low-Risk types are detected in exorbent warts, warts, and low-grade cervical intraepithelial lesions. High Risk HPV genotypes are present at high grade intraepithelial lesions, mainly of squamous cervical epithelium and invasive cancers (Dunne et al., 2007). Persistent infection by certain types of HPV can cause cancer and genital warts. The HPV 16 and 18 genotypes are responsible for the 66% of cervical cancers (Saraiya et al., 2015), 25% of high-grade intraepithelial cervical lesions and 50% of cervical dysplasias (Gudleviciene et al. al., 2010). The HPV types 6 and 11 are estimated to be responsible for about 90% of genital warts (CDC, 2017).

HPV infection is the most common sexually trans-mitted disease among developed countries nowadays

Table 1. Factors that contribute to the persistence and progress of the HPV infection and accelerate the risk of transition from HPV infection to oncogenesis.

•	**Factors related to the virus**
-	HPV Genotype
-	Incorporation of the virus
-	Viral load
-	Persistent HPV infection
-	Multiple HPV infection
•	**Factors related to the host**
-	Sexual behavior
-	Immune system
-	Maternal history
-	Hormonal factors
•	**Factors related to the environment**
-	Smoking
-	Sexually transmitted diseases
-	Contraception
-	Diet habits
-	Social factors
-	Economical factors

(Herrero et al, 2005). Global research studies have indicated that the highest incidence of the disease occurs in the female population, in women of reproductive age five to ten years after commencing their sexual activity (Muñoz et al, 2009). Clinical studies from the United States of America have shown that more than 50% of the male and female sexually active population, is expected to get an HPV infection at some point in their life. Moreover, the same researchers concluded that more than 80% of the female and male population is going to be infected by the age of 50 (Huang, 2008; National cancer institute, 2008).

Risk Factors

Epidemiological studies that have been carried out over the last 50 years, with the aim of determining the cause or causes of the cervical cancer, have indicated that there is no evidence of an agent solely as the cause of the disease. It is hypothesized instead, that a combination of factors is responsible for the oncogenesis. Bearing in mind that cervical infection by Hi-Risk HPV genotypes, is a necessary but not a sufficient prerequisite for the development of cervical cancer, it is very likely that other factors, in conjunction with HPV, contribute towards the development of HPV infection (Castellsagué et al, 2002; Shikary et al, 2009; Franceschi et al, 2009). Thus, factors related to the virus, host-related factors and environmental factors (Table 1), are estimated to have a significant role in the progression of HPV infection, contributing in its persistence and accelerating the process of carcinogenicity at the cervical epithelium (Wacholder, 2003; Trottier and Franco, 2006).

Risk Factors Related to the Virus

The main risk factor for the development of cancerous lesions at the uterine cervix is the persistent HPV infection by specific viral subtypes. HPV types 16 and 18 are both related to the squamous cell cervical carcinoma, while HPV 18 subtype is mainly associated with adenocarcinoma (Bekkers et al., 2004). It is estimated nowadays that 71.5% of all cases are due to the cervical infection by the HPV 16 and 18 subtypes, while the remaining 28.5% is associated with HPV 31, 33, 35, 45, 52 and 56. Furthermore, 90% of genital warts are related to the 6 and 11 HPV subtypes (Kanodia et al., 2007). At the same time, the likelihood of progression or regression of the HPV infection into cervical neoplasia, is directly related to the incorporation of the virus. Various research studies conducted to assess the relationship between HPV integration and carcinogenicity in the uterine cervix, revealing that the virus was integrated in 50% of cases of HPV 16 infection and in 90% of cases where the infection were associated with the HPV 18 subtype (Hopman et al, 2004; Hudelist et al., 2004; Andersson et al., 2005).

The correlation between the viral load at the level of the uterine cervix and the future development of cervical epithelial neoplasia, has not been accurately documented. It is not feasible with the current scientific data, to determine the exact value of the viral load that could be utilized as an index of future carcinogenicity in the uterine cervix (Sherman et al., 2003; Moberg et al., 2004). In contrast, the persistence of HPV infection in two or more visits, combined with the oncogenic dynamic of the responsible HPV subtype, undoubtedly increases the likelihood of progression of the infection to intraepithelial cervical dysplasia, or cervical cancer. It is estimated nowadays that infections lasting more than one to two

years, are the main cause of the development of both precancerous lesions and cervical cancer (Burchell et al, 2006; Schiffman et al., 2007; Woodman et al., 2007). Additionally, the infection with more than one HPV subtype, probably increases the duration of the disease and it is also estimated to amplify the likelihood of carcinogenicity in the uterine cervix (Mendez et al., 2005; Plummer et al., 2007).

Risk Factors Related to the Host

Sexual behavior – activity

Most of the epidemiological studies to date suggest that the development of the HPV infection in the uterine cervix, is directly related to the sexual behaviour of the individual. It is estimated that the age of commencing the sexual activity, as well as the number of sexual partners, influence the risk of developing dysplasias or intraepithelial neoplasms in the cervical epithelium. In particular, women who start their sexual life in an age prior to 16 years, have a higher risk of developing HPV infection than women who started their sexual activity at an older age. HPV infection is more common among sexually active adolescents and younger women and viral detection rates are gradually decreasing as the age increases. Thus, the incidence of the disease falls from 12% to 56% in women under the age of 21, to 2% - 7% in women over 35 years. (Winer et al., 2003; Scheurer et al., 2005; Moscicki, 2007).

In addition, possible factors that enhance the likelihood of the HPV infection in young women, seem to be the number of sexual contacts, the number of recent sex partners, and the number of companions that every partner had in the past (Ho et al, 1998). The increased incidence of HPV infection among young women is likely to be associated with the frequent rotation of sexual partners, which is common in these age groups. In 2007, Dunne and his colleagues in their study, indicated that the prevalence of the HPV infection rises from 19% in women with one partner within the last year, to 56% among women with six or more erotic comrades. Furthermore, the above mentioned authors in the same study revealed that both the HPV 6 and 16 subtypes had a detection rate of 1.3% in the studied sample, whereas the HPV 18 and 11 were detected at 0.8% and 0.1% respectively (Dunne et al., 2007).

Other Factors

The competence of the immune system, the number of term pregnancies and the hormonal profile of the women, are factors that are not directly related to the HPV, but, by common consent, contribute significantly to the persistence and progression of the HPV infection, playing a key role to the risk of transition from infection to carcinogenesis at the cervical epithelium. Studies have suggested that women who are immunosuppressed or immunocompromised, are more likely to develop HPV infection and dysplasias at the uterine cervix, than the general healthy population. Surveys involving HIV positive women indicate a higher risk of developing infections by multiple HPV types and cervical epithelial neoplasias, among the affected individuals (Gonçalves et al., 2004; Banura et al., 2008; Coelho Lima et al., 2009).

Moreover, the number of pregnancies in a woman's history, seem to be directly related to the appearance of cervical cancer. Multiple pregnancies, due to the maintainance of the transformation zone at the ectocervix for a considerable time span and due to the prolonged act of the elevated levels of progesterone on the cervix, are estimated to facilitate the development of HPV infection (Cai et al, 2008; Sarkola et al, 2009). However, unmarried women who do not have a history of term pregnancy, have an increased risk of infection by a high-risk HPV genotype, compared to women who have acquired a child (Cotton et al, 2007). Finally, endogenous hormonal factors, such as high estrogen levels, contribute to the oncogenic effect of the HPV on carcinogenesis of the uterine cervical epithelium (Brabin, 2002).

Risk Factors Related to the Environment

Smoking

Smoking, among the other harmful effects on human health, is also estimated to weaken the body's defense against the HPV. Nicotine detection in the cervical mucus among daily women smokers, at a multiple concentration than the one detecting in the blood stream, strengthens the hypothesis that there is a significant correlation between smoking and the vulnerability in acquiring an HPV infection, which increases the risk of developing cervical intraepithelial lesions and invasive carcinoma. It is commonly accepted that nicotine and its metabolites increase cell proliferation and cause neovascularization at the cervical epithelium among smokers positive for HPV strains. Furthermore, it is generally estimated that the HPV infection lasts longer among smokers, having a reduced chance of self-purification, compared to non-smoking women (Harris et al., 2004; McIntyre – Seltman et al., 2005).

Moreover, many research studies have revealed that smoking, whether active or passive, is an independent risk factor for carcinogenicity in the uterine cervix, but has not yet been fully elucidated at what stage of the process is being involved. Although smoking is not directly related to the occurrence of HPV infection, it is known to have immunosuppressive effects on the cervical epithelium of the uterus. It is estimated nowadays that polycyclic

aromatic hydrocarbons, among the most important carcinogens that are present in the cigarette smoke, form harmful contaminants in the DNA of the cervical epithelial cells, that may exhibit mutation of their oncogenes and tumor suppressor genes, leading to neoplastic transformation (Sarian et al., 2009; Collins et al., 2010).

Sexually transmitted diseases

Several micro-organisms have been associated in the past with the carcinogenicity process. Chlamydia, genital herpes and Ebstein – Barr Virus, have been implicated as risk factors for the onset of an HPV infection and cancer development at the uterine cervix. Recent studies have shown that chlamydia infection, by inhibiting the apoptosis of the cells containing them, enhances the likelihood of developing chronic and persistent HPV infection by Hi-Risk HPV strains, resulting to an increase risk of developing high-grade intraepithelial lesions and invasive cervical carcinoma (Clifford et al., 2005; Samoff et al., 2005; Samarawickrema et al., 2015).

Furthermore, studies that carried out in order to correlate Herpes Simplex-2 Virus (HSV-2) to carcinogenesis at the uterine cervix, indicated that there is not a clear correlation and that the Herpes Simplex Virus does not appear to be directly related to the occurrence of intraepithelial lesions and invasive cervical cancer (Zereu et al, 2007; Kwaśniewska et al, 2009). Similarly, Ebstein - Barr virus is estimated not to be directly related to the carcinogenicity of the cervical epithelium, but a co - infection with Herpes Simplex Virus is likely to increase the risk of developing cervical cancer (Szostek et al., 2009).

Contraception

The effect of steroid hormone contraceptives on HPV infection, at a molecular level, has not been fully understood to date and various studies were contacted with controversial results. These studies have been considered complicated, because there is a diversity of contraceptive pills and their use is periodically interrupted (Vaccarella et al, 2006). The correlation between hormonal contraception and carcinogenicity at the uterine cervix, is estimated to be significantly depended to the time period of their use. Thus, women taking contraceptive treatment for more than five years, have a double chance of developing future cervical cancer, compared to women who did not use contraceptive pills during their lifetime (Appleby et al., 2007).

Additionally, it has to be mentioned that the protection provided by the use of the condom against a potent HPV infection, is limited, although epidemiological studies urge that the use of male condom reduces the incidence of intraepithelial neoplasia and cervical cancer, regardless of the cell type (Scheurer et al, 2005; Baseman and Koutsky, 2005; Shew et al., 2006). Recent studies have revealed that women whose partner used condom regularly had about 70% less chance of developing HPV infection (Shew et al., 2006; Tobian et al., 2009; Van Howe, 2013).

Nutritional and socio – economical factors

The role of diet in the carcinogenesis of the cervix is not yet fully elucidated. The data of various researches are often conflicting and controversial. Several epidemiological studies associate the risk of developing cervical precancerous lesions and invasive cancer, with diets poor in fruits, vegetables and vitamins. Moreover, substantial alcohol consumption and the systemic use of tobacco are both estimated to significantly increase the risk of developing cervical intraepithelial lesions and cancer (Shannon et al, 2002; Hosono et al., 2010; Myung et al., 2011; Guo et al., 2015). Additionally, a study contacted in the United States of America, indicated that women aged 14 to 59, living below the poverty line, had a double risk of infection by High-Risk HPV types than women of higher socio-economical status (Kahn et al., 2007).

CONCLUSION

The synthesis of the evidence on major risk factors of HPV cervical infection providing possible categories contributes on the best practice and the assessment should be offered by the clinicians. The multiple risk factors related with the onset of HPV cervical infection could be possible categorized as factors related to the virus such as HPV subtype dominance, persistent HPV infection, HPV loading dose, and multiple HPV infection. The second category of factors related with the host behavior. There is a high risk of infection when sexual activities commencing on early age; existence of high number of sexual partners, which is the most salient risk factor; suppression and alteration of the immune status; the concurrent infection of other sexually transmitted diseases, an increasing number of lifetime sexual partners both in females and their male partners. The third group of risk factors included the environmental ones. The long – term use of oral contraceptives and smoking tobacco, have also been associated both with increased HPV prevalence. All these risk factors are deeply perplexing, with socioeconomic, cultural, and geographic variables. Previous reports highlight that all the risk factors involved in the continuous pathological process, of persistent HPV infection may lead to abnormal results of cytological examination, cervical intraepithelial neoplasia (CIN), and cervical cancer. This study is synthesizing evidence from

both clinical and systematic reviews. Another strength of this study is the categorization of the risk factors that could be easily recognized by all the clinicians. Limitations of this study are the heterogeneity in evidence extracted limits the ability to make conclusive recommendations regarding effective components of the HPV infection risk factors. Not being a prospective study is a drawback of the study, however the collection of evidence will be useful for making recommendations for future interventions in the detection of risk factors associated with the HPV cervical infections.

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