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Human Papilloma Virus Infection-Changes in Cervical Epithelium and Pathogenesis

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Abstract – There is excellent evidence that invasive carcinoma of the uterine cervix develops from abnormal cancerous surface epithelium i.e. carcinoma-in –situ. However cancer may develop from lesser degree of histological abnormalities or dysplasia. Etiopathogenesis of precancerous and cancerous lesions of cervix has received a great deal of attention past several decades. Large number of microbial agents was linked with its possible etiology. In early days even trichomonas was once considered as causative agents for carcinoma cervix. Later on numerous bacterial and viral agents were studied for their causative role. In 1970s HSV-II was thought to be implicated in abiogenesis of cancer. Further prospective studies measuring exposure to post HSV-II infection, however indicated no association for HSV-II with the process of cervical carcinogenesis. The most promising role of inducing cancer cervix now appearing is that of HPV. It has been found in recent studies that almost all if not all high grades CIN lesions and invasive cancer contain identifiable HPV DNA.

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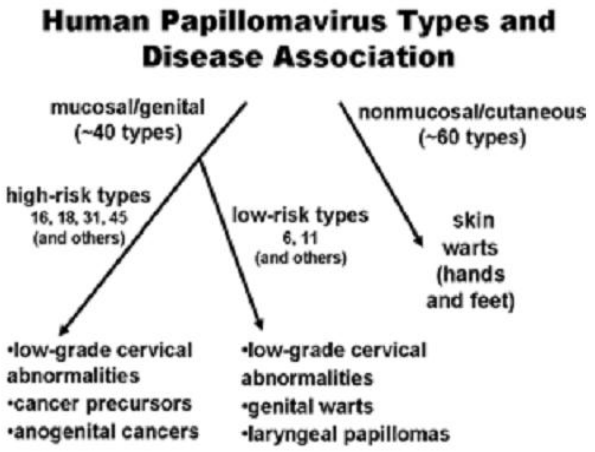
INTRODUCTION

Human papillomavirus (HPV) is one of the most common causes of sexually transmitted disease in both men and women worldwide and is thought to be the most common sexually transmitted viral disease in the United States. Genital HPV infection is not a reportable disease, so actual incidence and prevalence figures are not known; however, it is estimated that the incidence of new infections in the United States ranges from 1 million to 5.5 million per year, and the prevalence is estimated to be as high as 20 million. HPV continues to be an important topic, as rates of infection appear to continue to be rapidly increasing.

Papillomaviruses are ubiquitous and have been detected in a wide variety of animals as well as in humans and are specific for their respective hosts. More than 200 types of HPV have been recognized on the basis of DNA sequence data showing genomic differences. Eighty-five HPV genotypes are well characterized. An additional 120 isolates are partially characterized potential new genotypes. HPVs can infect basal epithelial cells of the skin or inner lining of tissues and are categorized as cutaneous types or mucosal types. Cutaneous types of HPV are epidermitrophic and target the skin of the hands and feet. Mucosal types infect the lining of the mouth, throat, respiratory tract, or anogenital epithelium. Based on their association with cervical cancer and precursor lesions, HPVs can also be grouped to high-risk and low-risk HPV types. Low-risk HPV types include types 6, 11, 42, 43, and 44. High-risk HPV types include types 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70. Included in the high-risk group are some HPV types that are less frequently found in cancers but are often found in squamous intraepithelial lesions (SILs). Some authors refer to these HPV types as intermediate-risk. Low-risk subtypes are also occasionally found in cervical carcinomas.

In addition to cervical cancer, HPV infection is also associated with anogenital cancers less common than cervical cancer, such as cancer of the vulva, vagina, penis and anus. The association of genital types of HPV with non-genital cancers is less well established, but studies support a role for these HPV types in a subset of oral cavity and pharyngeal cancers.

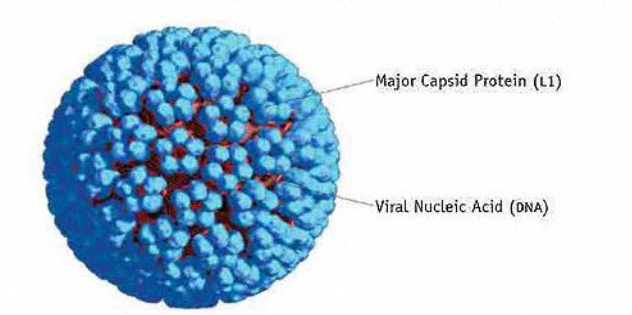


HPV-Associated Disease

Type	Women	Men
16/18	70% of cervical cancers	70% of anal cancers
	70% of anal/genital cancers	Transmission to women
6/11	90% of genital warts	90% of genital warts
	90% of RRP* lesions	90% of RRP lesions
		Transmission to women

* RRP = recurrent respiratory papillomatosis

THREE-DIMENSIONAL MODEL OF HUMAN PAPILLOMAVIRUS



HPV and cervical cancer

Overall HPV is responsible for 5.2% of all cancers. It is well established that HPV infection is the primary cause of virtually all cervical cancers and indeed deemed a necessary cause for the disease, without which, cervical cancer does not arise. A landmark study has shown that HPV DNA can be found in 99.7% of cervical cancer specimens. Worldwide, the plethora of HPV types causing cervical cancer varies from one country to another, however, over 70%, in any given country, are caused by only 2 types, HPV16 and HPV 18.

Infection of the genital tract by HPVs can initially result in low-grade lesions termed dysplasias or cervical intraepithelial neoplasia grade I. These lesions exhibit only mildly altered patterns of differentiation, and many of them are cleared by the immune system in less than a year. The mechanisms by which the cellular immune response clears HPV infections are still not clearly understood. Some of these lesions, however, are not cleared by the immune system and can persist for periods as long as several decades. Persistence of infection by high-risk HPV types is the greatest risk factor for development of genital malignancies such as squamous cell carcinoma or, less commonly, adenocarcinoma of the cervix . Cervical cancer is the second most prevalent cancer worldwide and is the fifth leading cause of cancer deaths in women . Approximately 470,000 new cases of cervical cancer are diagnosed yearly, with the mean age for the development of malignancy being 52 years. Risk factors for tumor development include persistent infection with high-risk viral types, a large number of lifetime sexual partners, coinfection with human immunodeficiency virus, immune suppression, and cigarette smoking.

EPIDEMIOLOGY

Just under half of the 100 HPV types identified infect the genital tract. Of these viral types only a small number have been detected in malignant lesions—that is, HPV 16, 18, 26, 27, 30, 31, 33–35, 39, 40, 42–45, 51–59, 61, 62, 64, 66–69, and 71–74. HPV 16 is the most malevolent and has been found in about 50% of cervical cancers throughout the world. Many other HPV types are responsible for benign warts, two of these types include HPV 6 and 11. There are geographic differences in the prevalence of HPV types in different regions worldwide. In Western Africa, HPV 45 is more prevalent, while in Central and South America HPV 39 and 59 are clustered, and in the Pacific Basin types 52 and 58 are dominant. Permeating through these clusters of potentially oncogenic types of HPV is the disproportionate higher prevalence of HPV 16. HPV infection has been increasing since the 1960s and is thought to be do to the increased use of oral, rather than barrier, forms of contraception. As HPV has been identified in 90% of cervical cancer, it is considered to be a risk factor of significant importance in the development of this malignancy. Other risk factors for the development of cervical cancer are elucidated.

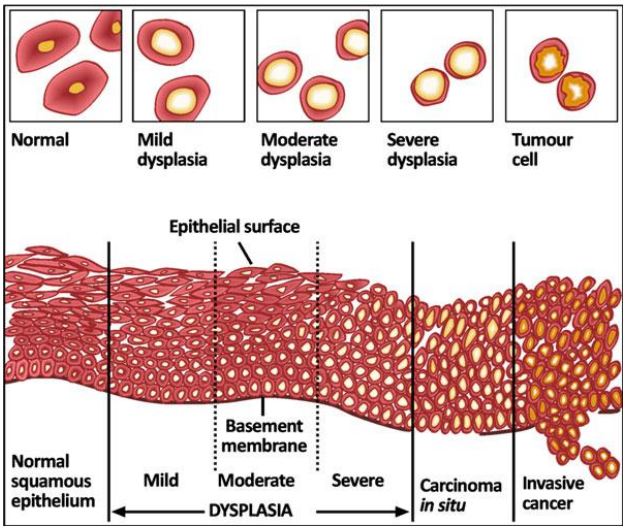
Cervical cancer Risk factors

- Increased number of sexual partners.
- Increased frequency of intercourse.
- Early age of first intercourse.
- Prostitution.
- Sexual behaviour of male partner.

Associated risk factors

- Tobacco smoking (nicotine metabolites identified in cervical mucus of female smokers).
- Use of oral contraceptives.
- Infection with other sexually transmitted diseases.
- High parity.
- Lack of certain nutritional factors (that is, as vitamin C or β-carotene).

Subtypes share less than 50% genomic homology with other HPV types and by having less than 90% homology in the nucleotide sequence of genes E6, E7, and L1 open reading frame with other papillomaviruses.



ROLE OF THE PAP SMEAR

The Papanicolaou smear is based on the work of a Greek physician, George N Papanicolaou. Papanicolaou first began to study normal and abnormal vaginal cytology in the 1920s. He published his findings with Herbert Traut, a gynecological pathologist, in 1941 in *The diagnostic value of vaginal smears in carcinoma of the uterus*. Named after its creator, today the vaginal smear is known as the PAP smear.

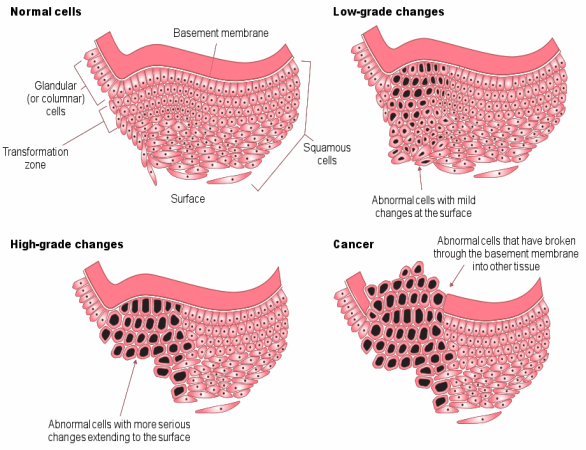
Unfortunately, there has never been an evaluation of PAP smear screening in a randomized control trial. The data regarding screening is based on differences seen geographically over the time that the PAP smear has been used. Overall, the PAP has decreased the rate of stage II squamous cell carcinoma in women that are regularly screened but has not been shown to decrease the rate of adenocarcinoma or adenosquamous carcinoma. The American College of Obstetrics and Gynecology recommends that PAP smear screening should start at age 18 or when the woman becomes sexually active. The recommendation is to continue annual screening until three normal PAP smears have been obtained; at this time, if the physician prefers, the women may be tested less frequently. There is no consensus as of yet at to what age to stop PAP smear screening, but since cervical cancer may be diagnosed postmenopausally, individual risk factors must be taken into consideration. The American Academy of Family Physicians recommends discontinuation of PAP smear screening after age 65 if the woman does not have a history of positive PAP smears. In women who have had hysterectomies the incidence of cervical cancer is extremely low. Therefore if the uterus was removed for benign reasons, the cervical epithelium was completely removed, and the woman had no previous abnormal PAP smear findings, screening may be discontinued.

PATHOGENESIS

HPV infection occurs at the basal epithelium. Although the incidence of infection is high, most infections resolve spontaneously. A small proportion of infected persons become persistently infected; persistent infection is the most important risk factor for the development of cervical cancer precursor lesions. The most common clinically significant manifestation of persistent genital HPV infection is cervical intraepithelial neoplasia, or CIN. Within a few years of infection, low-grade CIN—called CIN 1—may develop, which may spontaneously resolve and the infection clear.

Persistent HPV infection, however, may progress directly to high-grade CIN, called CIN2 or CIN3. High-grade abnormalities are at risk of progression to cancer and so are considered cancer precursors. A small proportion of high-grade abnormalities spontaneously regress. If left undetected and untreated, years or decades later CIN2 or 3 can progress to cervical cancer.

Infection with one type of HPV does not prevent infection with another type. Of persons infected with mucosal HPV, 5% to 30% are infected with multiple types of the virus.

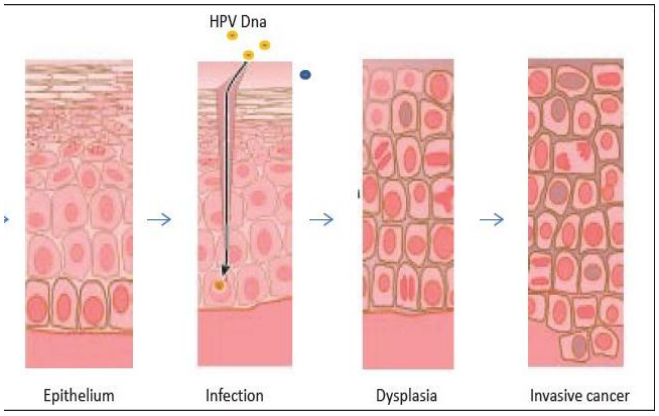


CONCLUSIONS

On the basis of the epidemiological and molecular evidence implicating high-risk HPV types (acquired through sexual contact) in the development of cervical carcinoma and its precursors, the International Agency for Research on Cancer, part of the World Health Organization, has classified HPV 16 and 18 as carcinogens in human beings. The data

accumulated so far underline the need for HPV-based diagnostic and screening tests, and the eventual development of prophylactic HPV vaccines.

In conclusion, HPV is a significant public health problem as a sexually transmitted disease and more importantly as a crucial contributing factor to the development of cervical cancer. Consequently, PAP smear screening has become a crucial part of women's health as early detection of cervical dysplasia has significantly reduced the morbidity and mortality of cervical cancer . Therefore, it is not only necessary for physicians to continue PAP smear screening on women who present for the “annual well women exam”, but it is also vital to target women who present to the clinic for other health problems; women who would otherwise not be screened for potentially devastating sequelae.



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