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HPV Caused Cervical Cancer

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Abstract

The causative role of human papillomavirus (HPV) in all cancers of the uterine cervix has been firmly recognized biologically and epidemiologically. Most cancers of the vagina and anus are likewise caused by HPV, as are a fraction of cancers of the vulva, penis, and oropharynx. HPV-16 and -18 account for about 70% of cancers of the cervix, vagina, and anus and for about 30–40% of cancers of the vulva, penis, and oropharynx. Other cancers causally linked to HPV are non-melanoma skin cancer and cancer of the conjunctiva. Although HPV is a necessary cause of cervical cancer, it is not enough cause. Thus, other cofactors are necessary for development from cervical HPV infection to cancer. Long-term use of hormonal contraceptives, high parity, tobacco smoking, and co-infection with HIV have been identified as established cofactors; co-infection with Chlamydia trachomatis (CT) and herpes simplex virus type-2 (HSV-2), immunosuppression, and certain dietary deficiencies are other probable cofactors. Genetic and immunological host factors and viral factors other than type, such as variants of type, viral load and viral integration, are likely to be important but have not been clearly identified [1].

Keywords: *Uterine cervix, oropharynx, conjunctiva, Chlamydia trachomatis, non-melanoma skin cancer*

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INTRODUCTION

Cervical cancer is the second most common cancer in women worldwide, and knowledge regarding its cause and pathogenesis is expanding rapidly. The common cause is persistent infection with one of about 15 genotypes of carcinogenic human papillomavirus (HPV).

There are four major steps in cervical cancer development: infection of metaplastic epithelium at the cervical transformation zone, viral persistence, progression of persistently infected epithelium to cervical precancer, and invasion through the basement membrane of the epithelium. Infection is extremely common in young women in their first decade of sexual activity. Persistent infections and precancer are recognized, typically within 5–10 years, from less than 10% of new infections. Invasive cancer arises over many years, even decades, in a minority of women with precancer, with a peak or plateau in risk at about 35–55 years of age. Each genotype of HPV acts as an autonomous infection, with differing carcinogenic risks linked to evolutionary species. Our understanding has led to improved prevention and clinical management strategies, including improved screening tests and vaccines.

The new HPV-oriented model of cervical carcinogenesis should gradually replace older morphological models based only on cytology and histology. If applied wisely, HPV-related technology can minimise the incidence of cervical cancer, and the morbidity and mortality it causes, even in low-resource settings[1].

THEORY

Cancer

Cancer is a disease in which the body cells become abnormal and divide without control. Cancer cells invade nearby tissues and they may spread through the blood stream and lymphatic system to other parts of the body.

Definition of HPV

Human papillomavirus (HPV) is a virus that can be passed from person to person through skin-to-skin contact.

More than 100 types of HPV have been found. More are harmless, but about 30 of these types infect the genital areas and you get them through sexual contact with an infected partner. Usually the body fights off HPV before it can cause health problems, if it is not cleared then they may lead to either low-risk or high risk factors.

Low-risk HPV types (6, 11, 42, 43, and 44) can cause genital warts in both men and women. These are soft growth on the skin and mucus membranes of genitals. They may also be found on the penis, vulva, urethra, vagina, cervix, and around and in the anus. Warts are not life threatening, but can be emotionally hard for a person to deal with[2].

High-risk HPV types (16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 73) can lead to cancers of cervix, vulva, vagina and anus in women. In men it leads to cancers of anus and penis.

HPV is a very common virus. It is more common in young men and women in their late teens and early 20s. Some researches suggest that at least three out four people who have sex will get a genital HPV infection at some time in their lives.

IS HPV MORE COMMON IN WOMEN OR MEN?

HPV is just as common in men and women. But HPV is less likely to cause serious health problems in men. Most men with HPV never get symptoms or health problems from it. There is no approved test for HPV in men. HPV and genital warts are just as common in native women as in women of other ethnicities.

Cervical cancer is less common in native women than in African-American and Hispanic women. But cervical cancer is more common in native women than in white women.

In United States, about 12,000 women get cervical or other genital cancers from HPV every year.

And about 7,000 men get head, neck and anal cancers from HPV every year. HPV and genital warts are just as common in native women as in women of other ethnicities.

TRANSMISSION

HPV is primarily spread through vaginal, anal, or oral sex, but sexual intercourse is not required for infection to occur. HPV is spread by skin-to-skin contact. Sexual contact with an infected partner is the most common way the virus is spread. Like many other sexually transmitted diseases, there often are no signs and symptoms of genital HPV infection.

YOU CANNOT GET HPV FROM

- Toilet seats;
- Kissing, hugging, or holding hands;
- Being unclean;
- Sharing food or utensils, Family history.

WHAT DISEASES DOES HPV INFECTION CAUSES?

- Approximately 12 types of HPV cause genital warts. These growths may appear on the outside or inside of the vagina or on the penis and can spread to nearby skin. Genital warts also can grow around the anus, on the vulva, or on the cervix.

- Approximately 15 types of HPV are linked to cancer of the anus, cervix, vulva, vaginal and penis they also can cause cancer of the head and neck. These types are known as "high-risk types" [3].

Cervical cancer begins in the women's cervix. It is the narrow organ at the bottom of the uterus that connects to the vagina. And in the same way it can grow on other body organs.

HOW DOES HPV CAUSES CANCER OF CARVIX?

The cervix is covered by a thin layer of tissue made up of cells. If HPV is present, it may enter these cells. Infected cells may become abnormal or damaged and begin to grow differently. The changes in these cells may progress to what is known as precancer. Changes in the thin tissue covering the cervix are called dysplasia or cervical intraepithelial neoplasia (CIN). In most women, the immune system destroys the virus before it causes cancer. But in some women, HPV is not destroyed by the immune system and does not go away. In these cases, HPV can lead to cancer or, more commonly, precancer[4].

Types of Cervical Cancer

There are mainly two types of cervical cancer. They are distinguished by the appearance of cells under a microscope:

a. Squamous cell carcinoma,
b. Adenocarcinoma.

Squamous Cell Carcinoma

Begin in the thin flat cells that line the bottom of the cervix. This type of cervical cancer accounts for 80 to 90 percent of cervical cancer.

Adenocarcinoma

Develop in the glandular cells that line the upper portion of the cervix. These cancers make up 10 to 20 percent of cervical cancer.

Sometimes both types of cells are involved in cervical cancer, other types of cancer can develop in the cervix, but these are rare. Like metastatic cervical cancer, they spread to other parts of body.

Symptoms

When present, common symptoms of cervical cancer:

Normally appear in the form of a cauliflower like growths, may also be flat they can be found on the inside and the outside of the vagina. These growths may take weeks or even an year to show after having sex with an infected partner [5].

Vaginal Bleeding

This includes bleeding between periods, after sexual intercourse or postmenopausal bleeding.

Unusual Vaginal Discharge

A watery, pink or swelling discharge is common.

Pelvic Pain

Pain during intercourse or at other times may be a sign of abnormal changes to the cervix or less serious condition.

Signs of Advanced Stages of Cervical Cancer

- Cervical cancer may spread within the pelvis, to the lymph nodes or else, where in the body signs of advanced cervical cancer includes:
- Weight loss,
- Back pain,
- Leg pain or swelling,
- Involuntary, ongoing release of urine or feces,
- Bone-fracture,
- Fatigue[6].

Screening Tests for Cervical Cancer

It usually takes years for cervical cancer to develop. During this time, HPV infection can cause cells on or around the cervix to become abnormal which may lead to cancer.

The two cervical cancer screening methods are:

a. Pap test,
b. HPV test.

Pap Test (Sometimes called cervical cytology screening)

- The Pap test is one of the most reliable and effective cancer screening methods available for women. It checks for changes on your cervix so that problems can be found and removed before they turn into cancer.
- Here in the Pap test, the health care provider will use a swab to collect cells from your cervix and check under a microscope for any problems.
- Women should start getting Pap tests three years after the first sex, or by age of 21, whichever comes first.
- Women should get Pap test at least once every three years.

HPV Test

- HPV test may also be used with the Pap test in certain cases. The HPV test looks for HPV, the virus that can cause cell changes in the cervix.
- The HPV test can identify 13–14 of the high-risk types of HPV[7].

HPV Vaccine against Cervical Cancers and Genital Warts

The vaccine has been widely tested in girls and women. It is safe and has no side effects. The most common side effect is soreness in the arm.

There are two types of HPV vaccines namely:

a. Cervarix,
b. Gardasil.

Cervarix

- It is a 3-dose series.
- Only to females.
- Female: 11 or 12 years of age. This age group has the best response to the vaccine, and the vaccine must be given before sexual activity begins. HPV vaccine can be started at 9 years. It is also recommended for females aged 13 through 26 years who have not been vaccinated.
- Prevents most cases of cervical and anal cancer in females if the vaccine is given before a person is exposed to HPV.

Gardasile

- A series of 3-dose series given for both males and females.
- Female and male: 11 or 12 years of age. This age group has the best response to vaccine, and the vaccine must be given before sexual activity beings. HPV vaccine started at 9 years. It is recommended for females aged 13 through 26 years who have not been vaccinated or did not finish the 3-shot series.
- It is also recommended for males aged 13 through 21 years who have not been vaccinated or did not finish the 3-shot series. It may be given to males aged 22 through 26 years and should be given to high-risk males aged 9 through 26 years [8].

BIOLOGICAL MECHANISMS OF HPV CARCINOGENESIS

In previous decades, our understanding of cancer pathways was rudimentary and often incorrect. In the face of such uncertainty, arguments based on assumptions of molecular biology were not particularly convincing. However, with the large body of work now available it is possible to develop a reasonable understanding of the ways in which cancer may develop and ways in which HPV infection can drive the process. Thus, we can say with some confidence that it is

plausible for HPV to cause cervical cancer and, furthermore, we can describe with reasonable clarity the general steps by which HPV may do so. Of course there is a lot of detail still to be revealed, but we are well on our way to a factual basis for understanding carcinogenesis rather than the guesswork and rudimentary models of just two decades ago.

What follows is a description of selected information that may illuminate salient aspects of the natural history of HPV and reasons why a mostly benign infectious process sometimes results in malignancy. It must be understood by readers that the pathways are based on extensive experimentation in biopsied human tissues, in tissue culture, and other kinds of molecular biology systems. However, many details of pathway modifications and aberrant pathway effects are speculative; they have not been shown to occur inside the relevant precancerous and cancerous tissues of living hosts. However, despite the many holes and inconsistencies, the models are still quite compelling and cohesive in facts. In future, we expect to see these molecular models being tested in human subjects.

Essentially all HPV types produce warty lesions but only high risk types promote the development of cervical cancer to any appreciable extent. Such differences between HPV types may seem surprising, given the high DNA and structural similarities. However, a large functional divergence caused by small genetic changes is the norm in many biological systems. Variations in carcinogenic potential among HPVs are principally governed by the E6 and E7 proteins; specifically by the capacities of these proteins to interact with and alter or destroy key cell cycle regulatory molecules.

The progress and outcome of an HPV infection depends on HPV type, anatomical location, and the nature and timing of local cellular and tissue influences. Virions access basal and parabasal cells in areas of erosion and viral DNA enters the cell nuclei. Establishment is tied to the tissue proliferative activity of epithelial cells and, in the case of extensive tissue repair; the viral infection can become widely disseminated. Persistence in keratinocytes is variable and related to viral type. Finally, integration of viral DNA may occur, resulting in lifetime persistence of certain viral genes in the cell. In the cervix, detectable infection by low risk HPV types is of relatively short duration, whereas infection by most high risk types lasts longer. On occasions, such infections may become persistent and last for years or even decades; it is in these cases that the risk of cancer is increased.

The establishment of HPV infection can be modulated by a competent and primed immune system. *In vitro* experiments have revealed an inverse association between the degree of cervical neoplasia and interleukin 2 production by peripheral blood mononuclear cells in response to HPV-16 E6 and E7 peptides. Women with CIN 3 or cancer appear to have a decreased ability to mount a T helper cell type 1 (Th1) mediated immune response to HPV E6/E7, compared with women with CIN 1 or HPV infected women without lesions. It is possible that a Th1 mediated cellular immune response could play a role in host immunological control of HPV infection and that lack of such an appropriate response may predispose to the progression of cervical disease.

If HPV enters immature metaplastic basal stem cells that are actively dividing the infection can become widely dispersed and persistent. In contrast, if infection occurs only in the parabasal transit amplifying cells the infection may become transient or

quasi-persistent. The size, histological grade, and duration of lesions can depend on the number and types of cells that become infected by HPV. In either transient or persistent infection there may be periodic viral genome amplification, depending on the activity of the infected daughter cells, which can lead to variable detection of the lesion by HPV DNA or Pap tests.

There is an important difference in host–virus interactions of carcinogenic HPV types and low risk HPV types; the former have activities that more strongly interfere with a set of host cell cycle control mechanisms. It is therefore useful to consider the effects of carcinogenic HPV types. HPV initially replicates to reach about 25–50 genomes/cell. The process by which this occurs is tied to the activities of four multifunctional viral proteins E1, E2, E6, and E7. One key activity of E7 is to overcome the pRB tumour suppressor block. Binding of E7 to pRB and its related members result in the liberation of E2F transcription factors, which play key roles in promoting host cell and viral DNA synthesis. E7 also binds and activates cyclin complexes, such as p33–cyclin dependent kinase 2, which control progression through the cell cycle. E6 protein can overcome the p53 protective control pathways, which are important in preventing the genetic damage that may lead to cancer.

HPV genomes attach to host chromatin via the E2 protein and replicate at a steady state, once for each cell division. It has been speculated that a benefit of this tethered theta mode of replication is that the loss of HPV DNA from cells by non-disjunction is minimised and the presence of low amounts of HPV DNA in cells is less likely to be detected by intracellular interference mechanisms that could trigger apoptosis. As cells differentiate and move to the surface there is a normal differentiation and maturation process that leads to pyknotic condensed cells that slough from the tissue. However, in virally infected tissues there is activation of unscheduled DNA replication in some spinous cells, accompanied by a switch in viral DNA replication to the rolling circle mode, which leads to the production of viral progeny. This reactivation of DNA synthesis can be detected by the presence of punctate proliferating cell nuclear antigen tissue staining (a protein with a key role in DNA replication) and the presence of HPV virions in a subset of upper layer cells.

HPV E7 proteins of both low and high risk types have an ability to promote unscheduled DNA replication in spinous cells. It is believed that the extent to which E7 stimulates cells, and the tissue location at which such stimulation occurs, is important to malignant progression. Spinous cells respond to E7 by the production of a cyclin kinase inhibitor, p21cip1, translated from sequestered RNA. In basal and parabasal cells existing mRNA for p21cip1 is not available and the protein is typically produced from new transcripts stimulated by p53; however, if p53 is inactivated by E6 the p21cip1 cannot be made. Spinous cells thus have a control advantage lacking in basal cells. Interestingly, high amounts of E7 can bind and block the activity of p21cip1. The relative amounts of E7 and p21cip1 are believed to determine whether cells re-enter S phase and replicate viral DNA or whether cells block viral production. The inspection of tissues reveals a mutually exclusive set of spinous cells with high amounts of either E7 or p21cip1. Cells in which E7 overcomes the p21cip1 block can become koilocytes and produce viral particles. This balance can explain the patchy expression of the HPV effect in infected tissues. A key function of the E6 oncoprotein is the destruction of p53, a protein that is activated upon phosphorylation via DNA damage sensing proteins. Activated p53 stops the cell cycle

in the G phase as a result of direct stimulation of p21cip1 by this molecule. Alternatively, in the case of major DNA damage or high amounts of viral replication, p53 may activate an apoptotic pathway. E7 also interferes with alternative non-p53 dependent apoptotic pathways. Thus, in the case of E6 mediated destruction of p53, cells are unable to prevent the accumulation of genetic mutations. Cells have other defensive homeostasis mechanisms, but E6 and E7 have counter functions that can lift the blocks and direct cells to enter S phase. Therefore, it appears that the development of malignancy is a consequence of an aberrant host-virus interaction. A potentially important event in this process is the aberrant regulation of E6/E7 expression. In low grade CIN lesions, E6/E7 expression is mainly found in differentiating spinous cells that have withdrawn from the cell cycle. In high grade CIN lesions and cervical carcinomas, strong E6/E7 expression is seen in the proliferating cell compartments.

HPV DNA is frequently incorporated into the host genomes in cancers in such a way that the E2 repressor protein is inactive and allows overexpression of E6 and E7. In cases where HPV integration is not detected, other mutations can be shown in the E2 protein or in repressor functions, such as YYI sites, which appear to allow continuous expression of the E6 and E7 oncoproteins. Yet another way in which E6 and E7 could be overexpressed in proliferating cells is by the generation of chimaeric HPV mRNAs encoding the E6 and E7 proteins that have host sequences at their 3' termini. Such RNAs are frequently more stable and allow more protein to be synthesized.

In persistent HPV lesions, viral genomes in the basal cells continue to stimulate the cells to ignore the DNA damage that may be accumulating. Cell stimulation by E6 and E7 of high risk carcinogenic HPV types produces clones with an extended life span that have passed a point called mortality 1 or M1, although the cells are still not immortal. An important step in immortalisation is related to telomeres. Normally, telomeres shorten every cell generation and once they reach a critical length the cells die. Telomere length is maintained by telomerase, which in combination with a capping function, can stabilize and even lengthen telomeres, allowing cells to continue dividing. E6 can activate telomerase and additional cell mutation(s) can then stabilize the telomeres and allow cells to pass a second stage called mortality 2 or M2. It is not known many additional independent mutations are needed to transform immortalised cells fully to malignancy. One set of mutations allows the cell to break through the basement membrane by eliciting a set of novel proteases. Another mutation(s) allows cells to move in the dermis. Undoubtedly, metastatic cells have accumulated many additional mutations that allow them to create their own microenvironment for survival in foreign parts of the body[9].

CONCLUSION

Cervical cancer screening has successfully decreased squamous cell cervical cancer incidence and mortality. The American Cancer Society (ACS) Guideline for the Early Detection of Cervical Cancer was last reviewed and updated in 2002; for the first time, those recommendations incorporated options including liquid-based cytology and human papillomavirus (HPV) DNA testing. Since that time, two vaccines against the most common cancer-causing HPV types have been developed and tested in clinical trials [2–7]. Numerous studies have been published on the efficacy of these vaccines, as well as issues related to policy and implementation[10].

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