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Human Papillomavirus Types and Cancer Screening Guidelines

Chandrika Johnson*

Department of Middle Grades, Secondary, and Specialized Subjects, College of Education, Fayetteville State University, Fayetteville, North Carolina, United States

***Corresponding author:** Chandrika Johnson, Department of Middle Grades, Secondary, and Specialized Subjects, College of Education, Fayetteville State University, Fayetteville, North Carolina, United States, Tel: (910)-672-1258; E-mail: chjohnson01@uncfsu.edu

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Abstract

Background: Human papillomavirus infection is a significant public health issue. The human papillomavirus is a group of DNA viruses. Human papillomavirus was first identified in the early 20th century, when it was shown that warts or papillomas could be transmitted in humans through direct physical contact. At first, the course of infection in people was unclear, but later the group of viruses was referred to as human papillomaviruses Types. There are over 100 known subtypes of human papillomavirus, each uniquely numbered according to slight differences in their genetic structure. The virus is separated into high or low risk types, depending on their association with (or lack of) cancer. Cancer Screening Guidelines. Hence, there is an essential need to target the types of human papillomavirus and know the cancer screening guidelines, which have been recently updated. Clinical Implications. Cancer screening is very beneficial because the problems can be treated early, before human papillomavirus ever turns into cancer. This is especially significant, as many HPV infections are asymptomatic, and since HPV infections are precursors to cervical cancer.

Conclusion: In this human papillomavirus review, the researcher focused on the various human papillomavirus-related infections, as well as human papillomavirus screening guidelines.

Keywords Human papillomavirus; Mucosal infection; Cutaneous infections; Cervical cancer; Nongenital

Introduction

Unlike other viruses (e.g. human immunodeficiency virus [HIV]), human papillomavirus (HPV) cannot survive in blood or other bodily fluids, but is limited to infecting the epithelial cells of the body [1]. Epithelial cells form the skin, with multiple layers forming the protective covering of the body, and the mucous membranes in the body, which line all the major organs and openings exposed to air to protect the internal organs against infections and diseases [2]. Transmission occurs when the infected cells of an individual come in contact with a small cut or abrasion on the surface of these barriers of an uninfected person, potentially resulting in some type of infection forming on the surface of the skin (cutaneous infection) or mucosal areas (mucosal infection) [3-5]. While the course of infection is determined primarily by the type of HPV [5,6], other factors contribute to the likelihood of serious infections or even cancer. A 2012 study indicated that while studies are mixed on what factors are significant, "young age at sexual initiation, inconsistent condom use, number of pregnancies, genetic factors, smoking, lack of circumcision of male partner, and oral contraceptive use" were reported as reasons one may develop symptoms of an infection [5]. Poor hygiene also has been noted as a risk factor for HPV-related infections. Bleeker et al. [7] indicated that circumcision would improve the personal hygiene and reduce subsequent risk of HPV-related infections and diseases in men.

The primary deterrent for developing HPV-related infections is the natural immune reaction to fight off any signs of the virus. Most people with healthy immune systems clear the virus from their body before any signs or symptoms of infection take place. Persons with weakened immune systems, however, caused by other diseases or conditions are more susceptible to developing persistent HPV-related infections [7-14]. The only way HPV infection can be confirmed is through specific DNA testing, with most people learning they are infected after symptoms (e.g. warts) have developed [15,16]. Since there is no cure for HPV, medical interventions currently focus on detecting and treating the symptoms of infection [2,15,17].

Although the epidemiology and natural history of HPV infection are well-documented in the literature, there is a gap in knowledge regarding preventive strategies, including vaccination, and screening methods [18]. Additional research focused on HPV transmission could inform future preventive strategies [18]. Research on HPV vaccination could examine long-term efficacy, correlates of protection, optimal age for vaccination, and delivery methods, particularly among populations that need it the most [18]. Finding the most efficient method of combining primary and secondary prevention will be critical for establishing optimal screening guidelines [18].

Types of HPV-Related Infections

The classification of symptoms and diseases caused by HPV are based on the type of virus causing the infection. As certain strains only infect the layers of the skin, the diseases associated with these HPV types are noted as cutaneous infections. The other types that affect the mucous membranes on the body are reported as mucosal HPV-related infections. While some mucosal infections can take place outside the genital area, such as in the openings of the nasal passage, around the eyes, and in the mouth, the lesions and risk for developing cancer are based on the HPV types and not the location. The following sections elaborate on these HPV-related infections and include the most recent update on the course of infection and appropriate terminology.

Cutaneous HPV-related infections

Researchers have identified over 100 subtypes of HPV; 60 types are limited to infections on the skin and are collectively referred to as nongenital HPV-related diseases. Nongenital cutaneous infections may cause noncancerous warts, which are the most common symptom, to form at or near the site of exposure [19,20]. Any area of exposed skin that is injured can become infected with these HPVs. The most common nongenital cutaneous diseases and HPV strains are listed in Table 1.

Nongenital Cutaneous Disease	HPV Type
Common warts	1, 2, 4, 27, 57, 63
Plantar warts	1, 2, 27, 57, 60
Flat warts	3, 10, 28, 41

Table 1: Nongenital cutaneous HPV-related diseases and associated HPV types [20].

The nongenital cutaneous HPV types are the primary cause of common skin warts. These warts are most likely to form on the hands and feet, but can also grow in other areas like the elbows or knees. Common warts usually go away on their own within a few months of exposure, yet some infections may last longer, depending on the health status of the person infected [21]. Plantar warts are small lesions that form on or around the soles of the foot, causing increased sensitivity in the heel of an infected person. While these warts may appear as corns or calluses, the main difference is the pain that occurs when pressure is applied on the site of infection [21]. Flat warts are most known for the lesions found on children and young adults, appearing in groups of raised flesh-colored bumps on the face, neck, backside of the hands, wrists, elbows, or knees. Each type of wart and treatment varies in part on the age of the person, with most infections clearing within 2-3 months depending on the extent of the infection [21].

Mucosal HPV-related infections

Approximately 40 HPV types infect the mucous membranes of the anogenital tract and other nongenital mucosal sites on the body. Mucosal cells are made up of epithelial cells and tissue, which accounts for their susceptibility to HPV infections upon exposure. Minor abrasions or small cuts in these areas are the primary entry mode of transmission, with the infected cells of one person coming in direct contact with similar cells of another susceptible individual [1,2,5,9,15,22].

Mucosal infections can produce a wide range of symptoms and diseases, with most exposures resulting in infections that are latent or asymptomatic [23-25]. One reason for these types of infections may be the exposure to low doses of HPV, rendering the virus unable to invade the body and cause further damage [15,16]. The lack of symptoms, however, does not guarantee the absence of infection, as the virus can lie dormant in some people for several weeks to months or even years [9]. This silent or hidden characteristic of HPV is what makes it so dangerous, as infected persons continue to spread the virus without knowing [3,16].

The virus is separated into high or low risk types, depending on their association with (or lack of) cancer. Infections with low-risk HPV types may go away on their own, cause benign warts or lesions to develop, or cause low-grade cellular changes that are not considered life-threatening [5,26]. Infections with high-risk HPV types may cause either low or high-grade cellular changes that, if untreated, over time may cause cancer [13,27-32]. Moscicki et al. [33] indicated that among the significant factors impacting the course of disease are the HPV type and persistent nature of the individual's infection. These authors added:

When a specific HPV type is found consecutively, it is very likely to represent the same variant as well, thus suggesting true persistence and not sequential infections [however] a major determinant of HPV persistence is how long the infection has already lasted the longer an HPV infection lasts, the more likely it is to last even longer.

However, the most important determinant of the type of infection following exposure to HPV is the particular strain of the virus that an individual contracts. While persistent infections are commonly reported as being necessary for more serious diseases, low-risk strains of the virus also can cause infections that last for extended periods of time. Although how long the infection lasts is important, the type of virus is what determines the chances of an individual developing cancer [5,28,29,33].

HPV-related infections that take place in the mucosal cells of the genitals are the most common sexually transmitted infection of HPV in the United States. Estimates of over six million men and women become newly infected with HPV each year [2,4,8,10,13,15,28,34]. Genital HPV is predominantly transmitted through penetrative vaginal or anal intercourse. However, transmission through genital contact without sexual intercourse is possible, with oral-genital and hand-genital transmission of some HPV types reported [1,2,22]. According to Fedrizzi [35], "HPV infection can also occur in approximately 8% of women who are not yet sexually active and approximately 20% in women who have had sexual activity with women only."

The types of HPV that are considered low-risk are the cause of genital warts (also known as Condyloma acuminate), the most common clinical manifestation of HPV-related infections. HPV types 6 and 11 in particular account for roughly 90% of all lesions that grow in the anogenital areas of men and women [9,15,36,37]. The primary mode of transmission is skin-to-skin contact with the infected cells in the genital region of another person. Genital warts appear most often in areas where friction occurs during intercourse, with lesions in men commonly found on the penis, scrotum, urethral meatus, and perianal area. Women may develop warts in the vagina, vulva, perineum, and perianal areas as well. Genital warts on the cervix or on the internal walls of the vagina do occur but rarely [5]. In some cases exposure to low-risk HPV causes warts to develop in the mouth or throat of a person who has had oral sex with an HPV-infected person. The size of genital warts varies, with some so small that they are not visible with the naked eye, and may appear as flat and flesh-colored or in groups that resemble cauliflower. While some people experience itching, burning, and discomfort from their lesions, it is also possible that warts may never appear [5,9,15,37]. Some people with low-risk HPV infections develop Recurrent Respiratory Papillomatosis (RRP), a rare disease that is "characterized by the growth of tumors in the respiratory tract caused by the human papillomavirus (HPV)" [38]. Hariri et al. [9] added:

There are juvenile onset and adult onset forms. The Juvenile Onset Recurrent Respiratory Papillomatosis (JORRP) form is believed to result from HPV infection transmitted perinatally from a mother to her baby during delivery. Estimates of the incidence of JORRP are relatively imprecise but range from 0.12 to 2.1 cases per 100,000

children aged <18 years. Even less is known about the incidence of the adult form of RRP.

While the warts that form are not cancerous, they are often difficult to treat, reappearing even after the course of treatment has been completed [39,40]. HPV types 6 and 11 are the cause of RRP, affecting an estimated 1.8 per 100,000 adults [38].

"Children born to mothers with genital warts are at risk for developing JORRP, with the reported relative risk of approximately 7 in 1000 births" [39]. Cesarean deliveries have been proposed as a way of eliminating this mode of infection, but studies noting the low incidence of JORRP and increased risks to the mother through surgery have all but eliminated this as a likely option [9,39].

Figure 1 illustrates the two ways that HPV infects the body (cutaneous or mucosal) and associated HPV types and diseases caused by each [5].

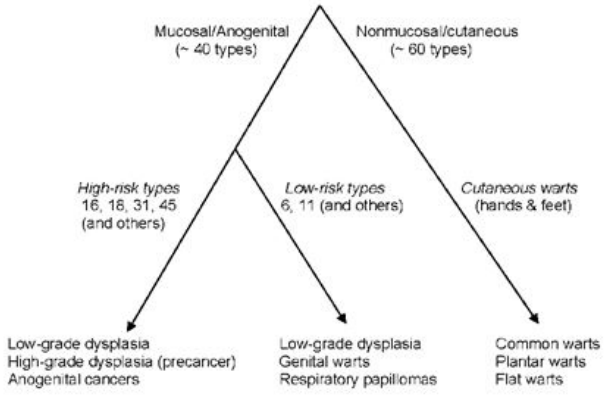

Figure 1: HPV diseases and associated subtypes [5].

Screening for HPV-Related Cervical Cancer

Screening of patients for early signs of cancer or HPV symptoms is aimed at increasing the likelihood they will not occur. A screening test is even better if it can detect precancerous or pre-invasive cells or changes, which can then be removed, preventing the development of invasive cancer. For example, the detection and elimination of precancerous changes in the cervix has led to a steady decline in the incidence of cervical cancer in the developed world over the last 40 years [41,42].

For cervical cancer, there are currently two types of screening available that use either a cytology-based test or HPV DNA/RNA testing. Since the 1940s, cervical screenings have centered on the technologies introduced with the Papanicolaou (Pap) test. The Pap test involves smearing cervical cells on a glass slide and then analyzing them under a special microscope to identify the presence of abnormalities, and the extent of abnormalities. The National Cancer Institute (NCI) [43] indicated that:

The main purpose of screening with the Pap test is to detect abnormal cells that may develop into cancer if left untreated. The Pap test can also find noncancerous conditions, such as infections and inflammation in regularly screened populations, the Pap test identifies most abnormal cells before they become cancer.

Researchers with the NCI [43] indicated that "death from cervical cancer is rare in women younger than 30 years and in women of any age who have regular screenings with the Pap test." Since the progression of most abnormal cells to precancerous lesions is gradual, this type of screening has been an effective method towards preventing cervical cancer worldwide [13].

At present, however, the traditional method of Pap testing (or smear) is being replaced with an automated liquid-based cytology test in the United States. Pap testing is the examination of cells from the surface of the cervix, performed to screen for cervical cancer or the changes that are understood to be forewarnings to cervical cancer. These forewarnings are called cervical high-grade squamous intraepithelial lesions (HSIL), or cervical intraepithelial neoplasia 2 or 3 (CIN 2 or CIN 3), also known as moderate or severe dysplasia. The automated liquid-based cytology test is performed by gently scraping cells off the surface of the cervix with a small brush or swab and dispersing them in a liquid medium. Both the traditional method and automated liquid-based tests are spread onto a glass slide, stained, and examined under the microscope by a pathologist. Data regarding both methods have shown similar rates of detecting abnormal cytology. However, a noted advantage of the liquid-based testing is that one cell sample can be co-tested or used with HPV DNA tests to detect high-risk HPV types [13].

The introduction of HPV DNA testing has advanced the sensitivity of cervical screening, as abnormal changes at the cellular level may be hard to detect histologically [44]. There is now increasing evidence from randomized clinical trials that carcinogenic HPV DNA screening is more sensitive than cytological screening for detecting histological CIN 3. However, two major considerations currently exist regarding DNA tests: (a) ability of the test to accurately detect the presence of infection (or lack of), and (b) whether the HPV types can be detected by the test.

The first refers to the issues surrounding sensitivity or specificity of a test. Sensitive tests yield positive results, which in turn, accurately reflect those infected with HPV. Highly sensitive tests are considered useful for population screening, as individuals with an infection are unlikely to be missed [45]. Specificity, however, is the ability of a test to confirm a true negative result. Therefore, a negative result from highly specific test means there is no presence of infection. A highly specific test is noted as more useful as a confirmatory test, in particular when a positive diagnosis may lead to harmful interventions [46].

On the other hand, the ability of an individual who is HPV infected or not to receive accurate results regarding his or her status is an important consideration with the use of these tests. More specifically, if a person infected with HPV gets a positive test result confirming his or her infection, that test is noted as having a high positive predictive value (PPV). The higher the PPV, the more confident clinicians can be in the course of action to take based on the positive result. Conversely, when someone is not HPV positive and receives confirmatory negative test results, the test is said to have a negative predictive value (NPV). The higher the NPV, the lower the probability of being infected at the time of the test. Therefore, the higher NPV of a test increases the confidence of course of actions (or lack thereof) based on a negative test. Schiffman et al. [13] wrote that:

Although a single negative high-quality Papanicolaou test does indicate a substantially lowered risk of cervical cancer lasting multiple

years, stronger reassurance of safety (i.e., a high negative predictive value) requires repeated rounds of screening to detect growing CIN 3 lesions…[a] high negative predic¬tive value permits safe and cost-effective lengthening of the cervical screening interval when HPV testing is used.

Saslow et al. [12] reported that, "several U.S. Food and Drug Administration (FDA)-approved HPV tests are commercially available, although none is yet approved for primary or stand-alone screening." The digene HPV Test [45] was the first FDA-approved HPV test in the United States that indicates if a woman had one or more of the following 13 high-risk HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. The digene HPV Test does not, however, identify the specific high-risk strains of HPV present. In 2009, the FDA-approved Hybrid Capture 2 assay (HC2) (Qiagen Corporation, Gaithersburg, MD), which targets the 13 HR-HPV genotypes and cross-reacts with HPV66 [46].

The cobas HPV test (cobas; Roche Molecular Systems, Pleasanton, CA) is another DNA test that has been approved by the FDA and identifies HPV 16 and HPV 18 separately, as well as detecting a group of 11 high-risk HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) and HPV type 66. In March 2009, the FDA announced approval of two new HPV DNA tests for clinical use in the United States. One test is marketed under the name Cervista™ HPV HR. The other test was designed to specifically detect HPV types 16 and 18 and is marketed under the name Cervista™ HPV 16/18.

Information from the Qiagen© website [46] revealed a list of recommendations based on the outcomes of one's HPV DNA test as follows:

If the HPV test shows you have a high-risk type of the HPV virus, but your Pap is normal, then the expert guidelines recommend that both tests be repeated in 12 months. If your HPV infection is still active at that time, and/or if your Pap is now abnormal, another exam called a colposcopy is needed to help determine if any "bad cells" are present. If abnormal cells are found early, before they become cancerous, treatment is highly effective.

If the HPV test shows you have a high-risk type of HPV, and your Pap result is abnormal or inconclusive ("ASC-US"), the expert guidelines say you should have a colposcopy exam right away.

Note that if the HPV test shows you do not have HPV, but your Pap looks abnormal, it is less likely that you have cervical disease. The presence of a high-risk type of HPV is necessary for cancer to develop. However, just to be sure, the guidelines recommend that you get a colposcopy exam of your cervix. And if you do not have HPV but your Pap results are unclear or inconclusive ("ASC-US"), both the HPV and Pap tests should be repeated in a year.

Cervical screening guideline update

Schiffman et al. [13] noted that throughout the United States: Clinical guidelines from professional medical organizations provide recommendations for cervical cancer screening, the management of women with an abnormal screening test, and treatment. These recommendations are usually developed through consensus meetings that review the evidence and, when possible, develop evidence-based guidelines. [however] cervical cancer screening is often viewed as a clinician–"patient" decision, not as a public program as it is in some other countries. The existing ACS guidelines for cervical cancer screening in the United States were recently updated "to address age-appropriate screening protocols, post-screening follow-up procedures and future considerations regarding HPV testing alone as a primary screening approach, and screening strategies for women vaccinated against HPV16 and HPV18 infections" [12]. A summary of these recommendations is listed in Table 2.

Age/Condition	Recommended Screening	Follow-up based on Results
Under 21	No screening	-
21-29	Pap testing (cytology) every 3 yrs, with	If (-) rescreen every 3 yrs
	no HPV testing for screening	If (+), follow ASCCP guidelines
30-65	HPV DNA & cytology (co-testing) every 5 yrs	-
	Cytology alone every 3 years	
Over 65	No screening after a negative screening result	-
Hysterectomy	No screening necessary	-

Table 2: American cancer society 2012 clinical screening guidelines for prevention and early detection of cervical cancer [12].

Saslow et al. [12] reported that the clinical screening outcomes included consideration of both the benefits and harm, the various methods of testing, and appropriate ages for their use. A notable change was that women should no longer be screened every year, regardless of their age or method of screening employed. Women would now be recommended to start screening at the age of 21 years, regardless of how old they were when they first had sexual intercourse. Support for this change was evidenced by the fact that yearly screenings only slightly decreased the detection and treatment of cervical cancer. With these low rates and associated costs lacking the justification of annual testing, the recommended intervals for screening were based on the age and history of each woman [12].

For women between 21 to 29 years old, Pap testing every three years was deemed clinically sound. Committee members consisting of individuals from the U.S. Preventive Services Task Force (USPSTF), the ACS, and the American College of Obstetricians and Gynecologists (ACOG) approved the Pap testing, noting that HPV testing by itself or as a co-test (with the Pap test), should not be used at any time for women in this age group. For women ages 30-65 years, the recommendation for co-testing with HPV DNA and cytology testing

was indicated as the preferred screening method. However, the Pap test alone every three years was noted as acceptable. The use of a Pap test without DNA testing for women between these ages was appropriate only for women with consistent negative cytology results. The HPV DNA/cytology co-testing was extended to five years (from three years) as studies increasingly show little significant difference in the rates of detection of advanced dysplasia (CIN 3) and cancers attributed to the use of these tests together. And while other countries are considering the use of HPV DNA testing as the primary method of screening (e.g. Netherlands), this was not recommended by the panel within the United States [12].

The recommendation that women 65 years and older no long need to be screened was maintained only if they had "3 consecutive negative cytology results or 2 consecutive negative co-tests within the 10 years before ceasing screening." Once women of this age were released from screening, they would never have to resume, even if (as noted by the committee) "they have a new sexual partner" [12].

Screening for women after being HPV vaccinated was considered by the committee, with no changes made to the current screening protocols. However, the growing efficacy of the approved vaccines (as described in the next section) may challenge the traditional models of testing and be unsuitable in the near future. As women who are currently being HPV vaccinated reach screening age, cell abnormalities typically detected by the Pap test will decrease substantially. This will negatively impact the Pap test's PPV and decrease the cost-effectiveness associated with this test. This is also a potential problem for the FDA-approved DNA tests and a leading reason why efforts should continue to advance the science of these tests [12,13].

Clinical Implications

Cancer screening can be very beneficial because the problems can be treated early, before HPV ever turns into cancer. This is especially significant, as many HPV infections are asymptomatic, and since HPV infections are precursors to cervical cancer. Early detection means finding early signs of disease, before they ever turn into cancer, which saves lives.

Conclusion

The history of HPV-related infections and classification of diseases began with the examination of the role of HPV in cervical cancer. One of the first methods for identifying the extent of infections was based on the abnormal cervical cell growth or dysplasia. The level of cervical cell growth or dysplasia was reported as mild, moderate, or severe, with cervical cancer the result of the most severe infections.

While the progression of persistent infections results in cellular changes from mild to severe, not all persistent infections will become cancer. This is because many questions remain unanswered about the exact natural history of HPV, including which types of infections persist to the point of becoming cancer and cancerous. It can take years for cancer to occur in a person who has HPV, and HPV cancer usually does not have symptoms until it is quite advanced, very serious, and hard to treat. Thus, it is important that healthcare providers get the word out about cervical cancer screening. Early cancer screening is a vital part of saving lives, as infections can be treated before evolving into cervical cancer.

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