**Human papillomavirus (HPV) is a sexually transmitted virus that has oncogenic potential.**

Non-oncogenic HPV infections include cutaneous warts and condyoma acuminata. HPV strains 16 and 18 are the specific oncogenic strains that can cause cervical, anorectal, oropharyngeal, vulvar, vaginal, and penile cancers. Cervical and oropharyngeal cancer are among the most prevalent of the HPV-linked cancers. HPV-induced cancers are preventable with the HPV vaccine if administered prior to initial sexual activity. HPV vaccine is highly recommended for pre-teens, teens, and young adults.

**Introduction**

Human Papilloma virus (HPV) is a group of over 200 viruses which are ubiquitous in the environment. HPV strains are often referred to as “non-oncogenic” or “oncogenic” (cancer-causing), based on whether they put a person at risk for cancer. Non-oncogenic HPV strains can cause cutaneous and anogenital warts which are treatable. However, oncogenic HPV viruses remain dormant in the body for many years prior to development of cancer. HPV viruses are either considered low-risk or high-risk depending on their likelihood of causing cancer. HPV type 16 and HPV type 18 are the high-risk strains most related to the development of cancer. Oncogenic HPV can cause cervical, anal, penile, vulvar, vaginal, and oropharyngeal cancers (Figure 1). HPV vaccine can prevent all of them.

**Figure 1:** Oncogenic HPV-related cancers: Annual Incidence Rate in U.S. as of 2021.
Epidemiology

Considered a sexually transmitted disease, HPV is spread through skin to skin, vaginal, anal, or oral contact. Persons with multiple sexual partners and those who do not use safe sexual practices are at the highest risk for infection. It is estimated that at least 80 percent of all men and women will contract an HPV infection sometime in their lifetime [1]. About 13 million Americans, including teens, become infected each year [2]. Each year in the United States, about 46,711 new cases of cancer are found in parts of the body where human papillomavirus (HPV) is often found: 25,689 among women, and 21,022 among men. Cervical cancer is the most common HPV-associated cancer among women, and oropharyngeal cancers (cancers of the back of the throat, including the base of the tongue and tonsils) are the most common among men [2].

Etiology and Pathophysiology

HPV can cause a variety of non-oncogenic and oncogenic diseases. Non-oncogenic HPV disease includes cutaneous warts and anogenital warts. Respiratory papillomatosis is a rare, airway HPV infection that can clear spontaneously or retain oncogenic potential. HPV is a double-stranded DNA virus that has a predilection for cutaneous and mucosal epithelium. Oncogenic strains of HPV release proteins that suppress the natural cell cycle checkpoints which block uncontrolled cell proliferation. The proteins affect DNA repair processes and impair G1 growth arrest, a natural point in the cell cycle where proliferation is inhibited. Cells enter the G1 growth phase of the cell cycle with unbridled continued which leads to unending cellular proliferation, eventual development of high-grade dysplasia, and progression to invasive carcinoma [1].

Non-oncogenic HPV diseases

Cutaneous Warts

Among dermatological diseases, warts are the most commonly reported disease associated with HPV. Cutaneous warts, referred to as verrucae vulgaris, are keratotic nodules that occur mainly on the hands and feet, especially on the soles of the feet (also called plantar warts). Those that proliferate externally on the face are called filiform warts. Verrucae vulgaris are caused by infection with HPV types 2a, type 27, or type 57, among others that are non-oncogenic [3]. Skin warts can be transmitted from person to person by close skin contact. The infection can also be transmitted indirectly from contaminated objects or surfaces, such as the area surrounding a swimming pool. Infection is more likely if skin is wet or damaged. It can take a cutaneous wart as long as two to six months to develop after your skin has been exposed to the virus. Over-the-counter medications that contain salicylic acid for topical application are effective. Dermatologists can treat cutaneous warts using various modalities such as liquid nitrogen, cantharidin liquid, shave excision, fluorouracil or imiquimod cream, laser treatment, or immunotherapy [4].

Anogenital Warts

Condyloma acuminatum (anogenital warts) is a sexually transmitted infection of the genital region in which HPV types 6 and 11 is detected. The disease is considered non-oncogenic and treatable. These warts typically appear in anogenital areas, such as the vulva, penis, groin, perineum, perianal skin, or mucosal surfaces. Condylomatous warts are skin-colored, cauliflower-shaped lesions, seen on moist genital surfaces. Anogenital warts may be accompanied by symptoms such as pruritus, burning, pain, and obstruction. Men who have sex with men (MSM) living with human immunodeficiency virus (HIV) are at disproportionate risk for high-risk HPV. Most condylomata are diagnosed clinically on the basis of their characteristic morphology and location. Condom use is only partially protective against HPV infection. Condyloma acuminata can be removed using a wide variety of modalities including δ-aminolevulinic acid-mediated photodynamic therapy (ALA-PDT), CO₂, pulsed-dye, Argon, Holmium, and Nd:YAG lasers, electrosurgery, or cryotherapy. Topical medications can also be administered by a health care provider. These include trichloroacetic acid, podophyllin, polyphenon E 10%, cidofovir, 5-Fluorouracil, and imiquimod. The HPV vaccine (Cervarix or Gardasil) is fully protective against these lesions [5].

Respiratory Papillomatosis

Recurrent respiratory papillomatosis (RRP) is a rare disease of the upper aero-digestive tract caused by human papillomavirus (HPV) infection, which affects children and young adults. It is largely considered non-oncogenic, however can predispose to squamous carcinoma. Papillomas usually appear as nodules that grow out from epithelium, primarily in the larynx, nasopharynx, tracheobronchial tree, and pulmonary tissue. The disease course is unpredictable, ranging from spontaneous remission to aggressive persistent or recurrent disease with potential for malignant transformation to squamous cell carcinoma. Clinically, RRP usually presents with nonspecific symptoms of airway involvement, including chronic cough, hoarseness, wheezing, voice change, stridor, and chronic dyspnea. Helical CT scan and bronchoscopy are methods of diagnosis. Currently surgery is the mainstay of treatment of RRP. However, Bevacizumab (Avastin), a VEGF monoclonal antibody, has shown promise as a systemic treatment for RRP [6] The HPV vaccine (Cervarix or Gardasil) is fully protective against these lesions.

Oncogenic HPV Diseases

Mainly the HPV type 16 and HPV type 18 are oncogenic strains considered high-risk types of HPV. Malignant HPV-induced neoplasms can present in the cervical, anogenital (anus, penis, vagina, vulva) and oropharyngeal regions.
**Cervical Cancer**

As the fourth most common gynecological cancer, cervical cancer has resulted in more than 300,000 deaths worldwide in 2020. HPV infections are commonly naturally eliminated by the body’s immune system within 2 years after exposure. According to most studies, less than 10% of women with long-lasting cervical HPV infection will develop cervical cancer [1]. HPV type 16 and type 18 oncogenes are significantly involved in the initiation and progression of 99% of cervical neoplasias. Genetic predisposition, exposure to other sexually transmitted diseases, immunosuppression, smoking, use of oral contraceptives, obesity, and the inflammatory microenvironment of the cervical region have been reported to be factors involved in the progression of HPV infection to cervical cancer [7]. The incidence of cervical cancer occurs most commonly in women over age 50. The signs and symptoms of cervical HPV are vaginal bleeding or abnormal discharge, but there may be no symptoms at all.

**Diagnosis**

Landmark European studies show that HPV testing alone provides a 60-70% greater protection against cervical cancer than Papanicolaou tests / Pap smear alone due to its increased ability to accurately determine the risk of precancerous or cancerous lesions [8]. Currently the US Preventive Services Task Force (USPSTF) and American Colleges of Obstetrics and Gynecology (ACOG) base their recommendations on that data. ACOG and USPSTF recommend triennial cytology (Papanicolaou tests) for women ages 21 to 29 years followed by either continued triennial cytology or adding a test for high-risk types of HPV every 5 years from ages 30 to 65 years. The task force also has endorsed a strategy of high-risk HPV testing alone every 5 years for women ages 30 to 65 years [9,10].

**Treatment**

Surgery, ablative or excisional treatments, and concurrent chemoradiotherapy are the standard-of-care treatment for cervical cancer. However, cervical cancer-related mortality remains high. The critical nature of cervical cancer treatment is underscored by the recent launch of the World Health Organization global initiative to accelerate the elimination of cervical cancer using a triple-intervention strategy of increased vaccination, screening, and treatment [11].

**Anal Cancer**

HPV-induced anal cancer is squamous cell carcinoma; a rare type of gastrointestinal cancer. It affects approximately 10,000 persons annually with approximately 1800 deaths per year. The high-risk subtype most likely to cause anal cancer is HPV-16 [12]. Risk factors include anal warts, HIV infection, multiple sex partners, receptive anal sex, anal fissures and fistulas, immunosuppression, and smoking. In patients infected with HIV, the risk of anal cancer is 40 times higher compared to the general population [13,14]. Men who have sex with men and women who have had cancer of the cervix, vagina, or vulva have increased risk of anal cancer [15]. Overall, it is diagnosed in slightly more women than men. Racial differences also exist; the incidence is highest in white women and Black men and lowest in Asian/Pacific Islanders. Anal cancer is also a cancer of older individuals with a peak in those aged 55-64 years and a median age for diagnosis of 60 years. Only 1.1% of anal cancers are diagnosed before age 35 [16]. Symptoms of anal cancer include anal bleeding, irritation, rectal prolapse, rectal pain, pelvic pain, bowel incontinence or flatulence; some individuals may be asymptomatic.

**Diagnosis**

Digital anorectal examination and cytology analysis are essential low-cost clinical tools for detection of lesions in the anal area. High-resolution anoscopy (HRA) is the current gold standard because of its ability to detect anal intraepithelial dysplasia (AIN) and premalignant high-grade squamous intraepithelial lesions (HSILs). However, there is a scarcity of trained providers who can perform this type of screening. The diagnosis of anal cancer is made by biopsy-proven histology [17].

**Treatment**

Recent research demonstrates that treatment of anal cancer should begin early when biopsy shows a precancerous growth termed high-grade squamous intraepithelial lesions (HSILs). Anal HSIL is the precursor of anal squamous cell carcinoma (ASCc). However, screening programs which include high resolution anoscopy and cytologic analysis are not widely available to diagnose this early stage. Additional research is needed to improve screening to identify anal HSIL. Several treatments have been used to treat high-grade squamous intraepithelial lesions, including topical imiquimod, 5-flourouracil, electrocautery, argon plasma coagulation, and radiofrequency ablation [18]. Immunotherapy agents such as pembrolizumab (Keytruda) and nivolumab (Opdivo) are being used in persons with more advanced anal cancer. Radiation therapy, particularly brachytherapy (internal radiation treatment), is also being used [19].
Oropharyngeal Cancer

The incidence of oropharyngeal cancer (OPC) related to infection with HPV is rising, making it now the most common HPV-related malignancy in the United States. HPV accounts for 71% of all oral squamous cell carcinoma (OPSCC) cases in the U.S. with HPV type 16 responsible for the majority. In both the UK and the USA, the incidence of oropharyngeal cancer in men has surpassed that of cervical cancer in women [20]. Oral sex is the risk factor for HPV+ OPSCC, with a strong association observed between number of lifetime oral sex partners and incidence of the disease. Areas of the mouth most commonly affected are the tonsils and base of the tongue. Symptoms include a long-lasting sore throat, earaches, hoarseness, swollen lymph nodes, pain when swallowing, constant irritation requiring clearing of the throat, and unexplained weight loss [21]. The most commonly affected individuals are White men between ages 50 and 65 [22]. There are no FDA-approved screening tests for HPV-positive OPSCC.

Diagnosis

Salivary rinse or swab tests for oral HPV DNA have been used in research settings to assess oral HPV infection among both cancer patients and healthy people. However, the sensitivity and specificity of these tests are unknown; there are many false positives and false negatives. After patients with cancer are treated, plasma circulating tumor human papillomavirus DNA (ctHPV DNA) is a sensitive and specific biomarker of recurrence human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC). This test may have utility for diagnosis in the future [23]. Oral exam with biopsy of suspicious lesions in the oral cavity are currently the methods used most often to diagnose HPV-OPSCC.

Treatment

The treatment of patients with OPSCC typically involves surgical excision, primary radiotherapy, or chemoradiotherapy. Transoral laser microsurgery (TLMS) and transoral robotic surgery (TORS) are commonly used techniques. Interestingly, prognosis for persons with HPV-positive OPSCC is better than those who have HPV-negative OPSCC [24].

Vulvar and Vaginal Cancer

Vulvar and vaginal cancer are rare disorders that account for 7% of all gynecologic malignancies. The most common HPV genotypes involved in these cancers are HPV 16, HPV 33, and HPV 45 [25]. Risk factors for persistent vulvar and vaginal HPV infection include smoking, immunosuppression, HIV infection, history of cervical cancer, and history of pelvic radiation. Women over age 65 are at highest risk for these two diseases. Symptoms include persistent itching, burning, and bleeding of the vulvar and vaginal area. Painful sexual intercourse or pain on urination can be signs of these cancers. The presence of masses, rashes, warts, or color changes of the membranes in the region are also signs [26]. The Pap test does not screen for vaginal or vulvar cancers. A pelvic exam and biopsy of lesions are the most common methods in which these cancers are diagnosed. Surgical methods both excisional and ablative techniques are used to treat these cancers. Cold knife, carbon dioxide (CO₂) laser, cavitation ultrasonic surgical aspiration, and electrosurgical loop excision are usually used for excision, while CO₂ laser vaporization, photodynamic therapy, and electrocoagulation (fulguration) have an ablative effect. Topical application of therapeutic agents such as imiquimod, an immunomodulator, can reduce the severity of lesions [27].

Penile Cancer

Penile cancer is a squamous cell carcinoma (PSCC) with the rare prevalence of 0.1-1 per 100,000 men in developed countries. However, it constitutes up to 10% of malignancies in men in some African, Asian and South American regions. It usually occurs in men over age 55 [28]. Risk factors for PSCC include the absence of childhood circumcision, phimosis (unretractable foreskin), chronic inflammation, poor penile hygiene, smoking, immunosuppression, AIDS, lichen sclerosus, ultraviolet light treatment for psoriasis, and infection with human papillomavirus (HPV) [29]. It can manifest as a hard mass, thickening of skin, ulceration, or sore that does not heal on the penis. Abnormal bleeding from the penis, red swollen areas, or white patches on the skin of the penis can also be the presentation. It often travels to the regional lymph nodes which may be enlarged in the groin. The treatment for penile cancer can include surgery, radiotherapy, chemotherapy, and immunotherapy [30].

Prevention of All HPV-Related Disease

Since HPV infection occurs most commonly after sexual activity, HPV vaccination is considered most effective in those who have not initiated sexual activity. Therefore, HPV vaccination is recommended for preteens age 11 to 12 years, but can be given starting at age 9. HPV vaccine also is recommended for everyone through age 26 years, if they are not vaccinated already. However, some adults age 27 through 45 years who are not already vaccinated can discuss vaccination with their health care provider about their risk and possible benefits. If vaccination is started before age 15, a two-dose schedule is recommended, with the doses given 6 to 12 months apart. For people who start the series after their 15th birthday, the vaccine is given in a series of three injections [31]. Three bivalent vaccines Cervarix®, Cecolin®, and Walrivax™, two quadrivalent vaccines Gardasil® and Cervarac®, and one nonvalent vaccine Gardasil® offer protection against high-risk HPV types 16 and 18, with additional protection against types 6 and 11 offered by quadrivalent vaccines [9].
Conclusion

Human papillomavirus (HPV) is ubiquitous in the environment. It is the most common sexually transmitted infection globally. Non-oncogenic HPV disease include cutaneous warts and anogenital warts. Respiratory papillomatosis is a rare, airway HPV infection that can clear spontaneously or retain oncogenic potential. The oncogenic strains of HPV; HPV 16 and HPV 18 remain dormant in the body for many years prior to development of cancer. HPV causes nearly all cervical carcinomas and is also a major risk factor for oropharyngeal, penile, vulva, vagina, and anal cancers. Since oncogenic HPV infection occurs most commonly after sexual activity, HPV vaccination is considered the most effective preventive treatment in those who have not initiated sexual activity. Health care providers should raise awareness among parents of preteens regarding this highly beneficial cancer prevention strategy.

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