Human Papillomavirus (HPV)

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Etiologic agent
The etiological agent is *Human papillomavirus*, which is a small, double-stranded circular DNA virus that infects the epithelium [1][2]. It comes from the genus *Peapillomavirus* which cause papillomas or benign tumors or warts that arise from the skin, mucous membranes, or glandular ducts [2][3]. More than 120 types of HPV are known to infect humans and animals and depending on the strand that sequences the outer capsid protein L1; some may be carcinogenic, 40 of which usually infect the mucosal epithelium [1][2]. This is especially the case in women’s health, i.e. cervical cancer.

Transmission
HPV transmission includes but is not limited to vaginal, anal, or oral sex with someone who has the virus. These are the common ways that the virus is spread through sexual contact [4]. Any skin to skin contact may spread HPV, but some research in 2014 at Brigham Young University say it is possible to transmit HPV through indirect means such as a medical instrument that may be considered sterile [5]. Another may include mother to infant at the time of birth, although this is of rare occurrence [1]. Regardless of transmission, symptoms may not always show to alert people that they or someone they know have the virus. This can lead to easier transmission for those who are not aware of having the virus.

Reservoirs
The only natural reservoir for HPV is humans. Other means are through synthetic measures [1]. The skin is its natural reservoir on humans since they infect epithelial cells, which can promote warts. The mucosa is also a prevalent area for HPV, especially in the cases of oral and vaginal mucosa. Oral HPV infection sometimes is easily seen by the growth of warts and is common, but infection of the vaginal mucosa can lead to cervical cancer. Though humans are the main reservoir for HPV particles, studies show that it is possible for those particles to live on
inorganic objects and, down the line, transmit the virus. But like other microorganisms that require hosts, they generally do not survive outside the human body [5].

**General characteristics of HPV**

HPV is a virus that affects the epithelial layer of specifically humans (hence Human Papillomavirus), most commonly associated with sexually transmitted disease or infection (STD/STI). A cure for HPV does not yet exist. Treatment is for the symptoms of HPV [6].

In a broader effect, the virus produces warts on the skin, wherever the infected area [2]. This includes nonsexual contact, but most cases of transmission are due to sexual contact. The HPV spread through nonsexual contact are generally different strains of HPV and are not the common HPV strains associated with sex [6]. HPV spread through sexual contact infects genital areas such as the vagina, the vulva including labia, penis, rectum, and anus.

Symptomatic responses are genital warts. These warts range from “cauliflower-like growths” that are easily seen to “hard and rough” or “soft and fleshy”; they are generally painless but may easily bleed or itch. Warts are generally small, being less than a quarter inch, but can grow into large warts, being more than an inch [6].

**Key tests for diagnosis and identification**

Doctors perform visual examination, sometimes by magnifying glass. This is for both sexes [6].

Pap smears help women determine pre-cancerous changes caused by HPV. Some new tests for HPV itself may help determine how to treat women with Pap smear anomalies [1][2][6]. But, these tests are not recommended for healthy individuals, for one, due to silent HPV infection that never cause health problems, and, for two, false negative results [6]. These second tests are usually for those who have shown abnormalities in their pap smears, which may indicate high risk HPV types and cancer [1].
In a laboratory, HPV DNA identified will determine if an infection is due to HPV. Assays have different sensitivities to specificity of HPV DNA. The FDA has approved many tests for high-risk HPV type in order to determine cervical cancer. However, these tests are not approved for men [1].

Polymerase chain reaction (PCR) assays help generate type-specific results. Epidemiologic studies target the L1 protein gene. The most used assays are virus-like particle (VLP)-based enzyme immunoassays. However, these tests are not standardized for consistent positive results [1].

**Signs and symptoms of the disease:**
HPV infections are often asymptomatic with no disease. This is the case of many of the 100 kinds of HPV, which cause no health problems. Signs and symptoms when symptoms are present “include anogenital warts, recurrent respiratory papillomatosis, cervical cancer precursors (cervical intraepithelial neoplasia), and cancers, including cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancer” [1]. Most low-risk infections will only have warts and symptoms most likely go away on their own. Usually warts appear within a few weeks up to 3 months after catching HPV [6]. Everyone develops different signs and symptoms and so appearance of warts doesn't necessarily mean they were recently infected. These warts can look different like cauliflower, be smooth, or be rough. They also range from a quarter inch in size to an inch or more [6].

**Historical information**
During the 1800s and before, cervical cancer was thought to be caused by a sexually transmitted disease [7]. However, Italian physician Rigoni-Stern in 1842, saw a relation of cervical cancer in married women, widows, and prostitutes, and rare in virgins or nuns. And so studies began. By the end of the 1960s, the first notion that the cause of cervical cancer was attributed to Herpes simplex virus (HSV), but it was discovered not to be the case. Once electron microscopy arose, the HPV genome was delved into more deeply.
In the 1980s, a group of the German Cancer Research Center found types of HPV in cervical tumors [7]. Zur Hausen was one of the scientists who had this theory [8]. Other scientists, supported by the National Cancer Institute (NCI) began to explore how HPV caused cancer, now they had great support that it could cause cancer [7]. HPV 16 and 18 were isolated and further epidemiological studies confirmed it. Other cancers subsequently such as anogenital and oropharyngeal cancers were attributed to HPV after further research. In 2008, Dr. Zur Hausen was awarded the Nobel Prize for the discovery of infection etiology of cervical cancer [8].

In the early 1990s Dr. Lowy and Dr. Schiller along with a laboratory supported by NCI, discovered the proteins that shell HPV could form a close resemblance of the original virus to promote the protective antibodies, but are safe due to the lack of viral genes. These VLPs helped create Gardasil and Cervarix, FDA approved in 2006 and 2009 [7].

**Virulence factors**

HPV virions infect through micro-abrasions. They have receptors like the alpha integrins and laminins, which help virions enter basal epithelial cells by clathrin-mediated endocytosis and/or caveolin-mediated endocytosis. Additionally, viral oncogenes, E6 and E7 help modify the cell cycle. This keeps the host in a state that favors amplification of viral genome replication, important to latent gene expression [9].

The E6 oncogene associated protein has ubiquitin ligase activity, leading to p53 proteosomal degradation. E7 act as primary transforming proteins and compete for retinoblastoma protein (pRb) binding sites. This frees up the transcription factor E2F to “trans-activate its targets,” helping push the cell cycle forward [9].

The most common manifestation of genital HPV infection is cervical intraepithelial neoplasia, or CIN. Low grade CIN infection may develop, but often resolves itself [1]. Higher grade CIN (CIN 2
or 3) presents a higher risk of progression of cancer and are considered precursors. Sometimes they can also regress, but if left untreated, cervical cancer can develop [1].

**Control/Treatment**

HPV infection currently has no solution for treatment. Most recourses are only management of symptoms that present itself such as the genital warts. Some have immune systems that can fight off the virus on their own, to prevent further infection of the epithelial layer. Signs may not present itself for many years, so the presence of symptoms may not indicate recent exposure to HPV.

For genital warts can be treated with topical creams, immune response modifiers (imiquimod and interferon alfa). For non-genital warts, anti-proliferative drugs (podofilox, podophyllin, and other chemo-destructive or kerotolytic agents) can be used [10]

There are also surgical options, generally for larger infected areas and cases. Cryosurgery, electrosurgery, and simple surgical excision are options. Often for high risk HPV, other surgeries include, carbon dioxide laser ablation, cavitron ultrasonic surgical aspiration (CUSA) or Mohs surgery, in which thin layers of the cancer containing skin are progressively removed until only cancer-free tissue remains [10] [11].

**Prevention/ Vaccine info, new trials**

Abstinence is the most effective way to prevent contraction of HPV. But for many people that are sexually active, condoms may reduce the risk of contracting HPV. Risk factors that increase the chance of obtaining the disease also include unsafe sex practices, which can be linked to multiple sexual partners, presence of other STDs, poor hygiene, nutrition, and other conditions that might suppress the immune system.

Pre-vaccination assessments such as Pap tests or screening for HPV can help prevent HPV from infecting someone. Ideally vaccines for HPV should be administered before being exposed.
Those who have been exposed are recommended to get the vaccination and will gain some benefits of the vaccine [1].

Three HPV vaccines are available in the US. These are non-infections subunit vaccines. The antigen is the L1 major capsid protein, which helps mimic the structure of the HPV virus, promoting antibodies to be created and released to counter it. However, it does not contain viral genes so there is no chance for infection of HPV [1].

Quadrivalent HPV vaccine was approved in June 2006 and is known as Gardasil. This is recommended for people from age 9 through 26 or those who have not had HPV virus or any other vaccine. This is administered in 3 doses. This has about a 99% efficacy [1].

Merck is another one approved in 2014, a 9 valent vaccine, similar to Gardasil [1].

Bivalent HPV vaccine known as Cervarix, was approved in October 2009. This is a vaccine geared towards females age 9 through 25. This is also administered in a 3 dose series. This is not recommended for males. This has about an 88% efficacy [1].

**Local cases or outbreaks (with incidence figures)**
HPV is the most common STI in the US. Approximately 79 million people between 15 and 59 years of age have HPV in the US [12]. 14 million new cases are diagnosed each year [12]. Roughly 340,000 to 360,000 women and men were affected by genital warts caused by HPV, before vaccines were introduced [13]. About 1 in 100 sexually active adults have genital warts at any given time [13]. More than 11,000 women get cervical cancer each year [13].

**Global cases or outbreaks (with incidence figures)**
In 2008, there were just over 500,000 new cases and about 275,000 deaths due to cervical cancer [14]. About 70% of cervical cancer cases are directly associated with HPV, but virtually 99% have a link to HPV [14].

More than 85% of cervical cancer deaths are in developing countries, where it accounts for 13% of all female cancers [14].

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