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HPV in Men: Prevalence, Transmission Dynamics, and Health Implications

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KEY WORDS

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ABSTRACT

Human Papilloma Virus (HPV) is a culmination of over 200 known viruses. Most of these strains of viruses do not have any negative effect on humans. There are a handful of known strains that are high-risk and if infected, could lead to common warts, genital warts, or even cancer. Human Papilloma Virus effects both men and women but research has a focus on women. In 2019, HPV caused an estimated 620,000 cancer cases in women and 70,000 cancer cases in men (WHO, 2024). There are many ways to protect oneself from infection, for example, limiting sexual partners, using protection such as condoms, and getting vaccinated. Currently, there are two vaccinations available for women and only one for men. Men rarely show symptoms and there is no way to test for the infection. With the lack of research and knowledge, most men are not vaccinated for Human Papilloma Virus. The transmission, prevalence, and health implications for Human Papilloma Virus in men is extremely under researched. The goal of this publication is to review the global and regional estimates of the overall, type-specific, and age-specific prevalence of genital HPV DNA in general populations of men. Hopefully, this paper will help drive more research to be conducted to fully understand and stop the spread of infection in men, which could aid in reducing the risk of developing penile, anal, and oropharyngeal cancer.

Introduction

Human Papilloma Virus (HPV) is a group of viruses that infect the cells on the surface of the skin, on the moist surfaces, or inner lining of some organs and body cavities, such as the cervix, vagina, vulva, penis, anus, mouth, and throat. The HPVs are members of the *Papillomaviridae* family, and there are five genera (alpha, beta, gamma, mu, and nu) with more than 100 genotypes. The HPV alpha genus infects cutaneous and mucosal epithelia and is associated with most cases of cancer (Chihu-Ampan, Pedroza-Saavedra, Gutierrez-Xicotencatl, 2023). HPV infections can cause abnormal tissue growth, such as skin or genital warts, and other changes to cells, including cancer (NIH, 2024). Human Papilloma Virus is the most common sexually transmitted viral infection in the world (Bruni et al., 2023).

The molecular structure of HPV consists of two capsid proteins L1 and L2, a histone, and circular, double stranded, genomic DNA. They are small non-enveloped icosahedral capsids that contain three oncoproteins E7, E6, and E5 that all play an essential role in cellular transformation. The degradation of p53 is induced by E6, inhibiting the cell cycle arrest and apoptosis, disrupting the essential cell functions. This process ensures DNA replication and survival of cells with severe DNA damage. E7 induces ubiquitination and degradation of the retinoblastoma protein (pRb) to maintain proliferative signals. E5 can promote cancer cell proliferation by interacting with the epidermal growth factor receptor (EGFR). Additionally, E5 inhibits apoptosis by increasing ubiquitination and proteasome degradation of the pro-apoptotic protein, Bax, and the

degradation of Fas receptors preventing the death domain formation (Chihu-Ampan, Pedroza-Saavedra, Gutierrez-Xicotencatl, 2023). These events induce the proliferation, immortalization, and malignant transformation of HPV-infected cells.

The structure of HPV has a significant impact on how it affects the body when it enters. It is known that the cell surface binds with virions mediated by the Heparan Sulfate Proteoglycans (HSPGs) but this process continues to be researched. This primary attachment depends solely on L1, while researcher Loonibha Shrestha suggests that L2 is involved in the early processes, but it is still unclear. A long delay in internalization is accompanied by changes in the mode of binding and a potential transfer to a secondary receptor. HPV is internalized via a clathrin-dependent endocytic mechanism, dependent on actin (Shrestha, 2022). Molecular detection of HPV implies prevalent infection, reinfection, auto-inoculation from the oral cavity, anogenital areas or intermittent viral shedding from a latent infection. Persistent infection by high-risk HPV types, is associated with oropharyngeal and anogenital malignancies in men and women (Sasidharanpillai et al., 2021). There are over 200 types of HPV with 12 being oncogenic; those types are 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 (NIH, 2023). The cancers involved with Human Papilloma Virus include cervical, anal, penile, and oropharyngeal (Bruni et al., 2023).

Background

Symptoms and Prevention

Human Papilloma Virus affects both men and women, but research has mostly focused on women. The physical symptoms that are

visible when infected with HPV are warts, especially genital warts when transmitted sexually. The most common symptom for HPV, like most sexually transmitted infections, is no symptoms at all (Mayo Clinic, 2021). This makes it difficult to diagnose and detect, therefore, preventative measures are particularly important. There are numerous ways to protect oneself from infection, for example, limiting sexual partners, using protection such as condoms, and getting vaccinated.

Currently, there are two vaccinations available for women and only one for men. Gardasil 9 is the vaccine available to both men and women. It is a non-infectious recombinant vaccine prepared from the purified virus-like particles of the major capsid, L1, protein of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, with seven of them being high-risk types of HPV. This vaccine is highly immunogenic and causes an antibody response towards HPV (Center for Disease Control (CDC), 2021). The Center for Disease Control and Prevention (CDC) recommends that children between the ages of nine and twelve receive the HPV vaccination, before sexual activity begins, when their risk of exposure is increased. The vaccine requires two doses that needs to be given six months apart and is the only vaccination available to the male population.

The Difference Between Males and Females with HPV

An HPV test for women is used to detect a cervical HPV infection but cannot detect precancer or cancer itself. The first HPV test occurs after a woman has her first sexual encounter and is repeated every five years. This is not to be confused with a Pap test. A Pap test is used to find cellular changes or abnormalities in the cervix and does not detect HPV. An HPV test is only available for the cervix and there is no other way to detect HPV in other areas. The need for HPV detection methods in men are numerous. There needs to be screening available to everyone in order to detect anogenital warts, recurrent respiratory papillomatosis, HPV-related cancer in men, and infertility.

Men infected with HPV rarely display symptoms and testing certified by the Food and Drug Administration (FDA) is still not available. Therefore, HPV-infected men could still transmit this virus to others without knowing. Approximately 45% of males ages 18 to 59 are currently carrying active genital HPV infections according to a study conducted in 2017 by JAMA Oncology (Fred Hutch Cancer Center, 2017). Research has shown that infection of HPV is higher in males than females. As females age, the HPV infection rate decreases but age has no effect on the rate of infected males, with the infection rate remaining at an elevated level (Fred Hutch Cancer Center, 2017). Due to the lack of research and knowledge, most men are not vaccinated against the Human Papilloma Virus.

The transmission, prevalence, and health implications of men infected with the Human Papilloma Virus is extremely under researched. It needs to be conducted to fully understand this virus and how to protect oneself through vaccination to stop the spread of infection. This could assist in reducing the risk of developing penile, anal, and oropharyngeal cancer in men, as well as cervical, anal, and oropharyngeal cancer in women.

Worldwide Research and Data on HPV in Men

There was a twenty-seven-year study conducted from January 1, 1995, to June 1, 2022, with a focus on men positive for HPV globally. The goal of the study is to update the global and regional estimates of the overall, type-specific, and age-specific prevalence of genital HPV DNA in general populations of men. The researchers gathered their data from a multitude of journals and articles with men over the age of fifteen from all over the world, who are vaccinated for HPV but with no HPV-related pathology. The data came from 5685 publications from database searches from 65 studies from 35 different countries that comprised a total of 44,769 men. These studies were heavily monitored and controlled by personnel from Embase, Ovid MEDLINE, and Global Index Medicus. The techniques used in these studies to gather their data consisted of PCR and Hybrid Capture 2. These techniques for HPV DNA detection were used to collect samples from penile or anal sites after 1995. Hybrid Capture 2 technology detects RNA-DNA hybrids using signal-amplified, chemiluminescent technology (Clavel et al., 1998). Because of their low sensitivity for HPV detection, urine and semen samples were used. The 65 studies provided data from 35 countries, with 16 countries having more than one study. Europe and Northern America accounted for 31 (48%) of the studies. No prevalence data were found from three SDG regions consisting of Northern Africa and Western Asia, Central and Southern Asia, and Oceania (excluding Australia and New Zealand). High-income countries accounted for 36 (55%) studies and only six (9%) studies were from low or lower-middle-income countries.

Of the 62 studies with information on date of specimen collection, 30 (48%) had samples collected before 2006, 25 (40%) between 2006 and 2013, and only seven (11%) from 2014 or later. 32 (49%) of 65 studies sampled at least the penile shaft and the glans of the penis or coronal sulcus. The most sampled genital anatomical sites were glans of the penis and corona sulcus (44 [68%] studies) and the penile shaft (32 [49%] studies); prepuce, foreskin, or frenulum (22 [34%] studies); the urethra or meatus (21 [32%] studies); and the scrotum (19 [29%] studies).

The estimated overall HPV prevalence of any type among men was 31% with study-specific prevalences ranging from 1% to 84%. The overall prevalence of high-risk HPV (HR-HPV) was 21% with study specific prevalences ranging from 1% to 75%. HPV-16 was found to be the most frequent HR-HPV type at 5% globally. Age-specific information was received after completion of 47 studies with a high prevalence of HPV in young adult men. People aged 25-29 years old for any HPV type was 35%, HR-HPV was 24%, and HPV-16 was 6%. HPV-16 age-specific prevalence curves for HR-HPV in Eastern and South-Eastern Asia, Europe, and North America for ages 15-20 years.

These studies had a median HR-HPV prevalence of 20% with significant heterogeneity. The estimated global prevalence for genital HPV infection among men is 31% for any HPV and 21% for HR-HPV according to the 65 studies conducted between January 1, 1995, and June 1, 2022. HPV-16 remains the most common oncogenic and preventable HPV type for both men and women globally (Bruni et al., 2023). This study shows that almost 1 in 3 men over the age of 15 are infected with at least one genital Human Papilloma Virus type, and 1 in 5 are infected with one or more of

what are known as high-risk, or oncogenic, HPV types (WHO, 2023).

The authors and researchers concluded that HPV prevalence in men peaked in the group aged 25–29 years and remained high until at least the age of 50 years. Prevalence in the group aged 15–19 years was also high, suggesting that young men are being infected rapidly following first sexual activity. These estimates are consistent with data from studies on the natural history of HPV infection in men, which show stable rates of detection of incident genital HPV across age groups and low seroconversion rates following HPV infection, suggesting that men remain susceptible to HPV infection across the lifespan. This age profile of infection in men is different from the profile in women, for whom genital HPV prevalence peaks soon after first sexual activity and declines with age, with a slight rebound after age 50–55 years normally after menopause.

The Relevance of Age

In a study conducted in 2013, the researchers implemented a genital swab test to collect their data. In this study, 1,800 adult men, both vaccinated and unvaccinated, were swabbed and tested for HPV prevalence. Results revealed that men aged 18 to 22, had the lowest rate of infection at 29%. The researchers hypothesized this was due to the younger generations receiving their vaccinations before their first sexual interaction. Men aged 23 and above had higher rates of infection (Fred Hutch Cancer Center, 2017).

Sexual Relations, Promiscuity, and Sexuality

A systematic review and meta-analysis of literature was conducted in 2018. There were sixteen articles used to gather all their data after weeding through errors, discrepancies, and duplications. The men studied were both English and Spanish, the number of years researched is unknown. After collection and analysis of data, a correlation between Human Papilloma Virus and sexual relations was discovered.

The studies found that the risk reduction is lowered in people who have their first sexual interaction later in life and with a stable partner. As the number of female sexual partners a male has increases, his risk also increases (Rodriguez-Alvarez et al., 2018). Anal cancer is the most common cancer in men that develops from an HPV infection (HPV Update Webinar 2024). Sexuality of a male has an influence on their risk of this virus. Homosexual males are more susceptible to anal cancer than heterosexual males. The risk is four to ten times increased in homosexual males than heterosexual. The correlation between genital HPV and sexuality is unknown and continuing to be researched.

A protective factor against HPV is male circumcision. Circumcision is a procedure that removes the foreskin of a male's genitalia. Research has shown that circumcised males have a prevalence lower by ten percent from uncircumcised males. The mechanisms by which circumcised men are less likely to become infected with HPV may be related to a reduction in the acquisition of new infection or to clarification of pre-existing infection, since the absence of foreskin may reduce the risk of auto-reinfection at the urethral site (Rodriguez-Alvarez et al., 2018).

The Future of Testing for HPV

There is only one way to test for Human Papilloma Virus: via cervical screening in women. There are several types of research experiments and trials currently being conducted to determine other ways to test women as well as to find ways to test men to slow down the spread of infection. The aim of one study was to investigate HPV DNA detection and genotyping on paired genital and urine samples and to evaluate if urine samples could be used to monitor HPV infection. The study was conducted in China from September 1, 2011, to June 30, 2012, with 250 patients including 203 females and 47 males. Agreement between paired samples showed that HPV detection had a significantly greater concordance in the samples obtained in females than males (Yang et al., 2023). Another study by Mario Poljak, Kate Cuschieri, Laia Alemany, and Alex Vorsters, stated that urine samples from males are less appropriate and accurate for the detection of anogenital HPV infections because the anogenital secretions "collected" by urination differ due to anatomical differences (Poljak et al., 2023). Urine appears to be an appropriate surrogate sample for HPV DNA detection in women, while the utility of urine for HPV DNA detection in males is less certain.

Blood is another resource to test for Human Papilloma Virus. It can contain detectable bio fragments that may be indicative of underlying or recurrent neoplastic disease. The detection of antibodies against the HPV-16 E6 protein in blood has been explored extensively in the last decade as a potential screening, diagnostic, and prognostic tool for the early detection and monitoring of HPV-AOC (Poljak et al., 2023). In a study by Warlow et al., the detection of HPV DNA in pretreatment plasma using ddPCR showed high (>90%) agreement with p16INK4a and the HPV PCR status of the pretreatment solid biopsy samples in oropharyngeal cancer patients. A recent meta-analysis on the performance of cHPV DNA in monitoring treatment response in 457 HPV-AOC patients showed a pooled diagnostic sensitivity and specificity of 65%.

Oropharyngeal cancer is a common HPV based cancer from both males and females. Saliva is not considered a robust specimen for HPV testing, nor are specimens obtained by swabbing or brushing tonsils or the oropharynx without visible lesions. One study compared oral gargling versus tonsil brushings in a sizeable age-stratified sample of oropharyngeal cancer-free individuals. It was found that HPV detection was difficult when using tonsil brushings from both children and adults. In contrast, HPV infection was detected more frequently in gargle specimens, particularly those of adults, but with poor agreement with the paired tonsillar sample (Poljak et al., 2023). Research for this continues, and with bigger populations, we can have a better understanding of using blood, plasma, urine, and saliva for HPV testing.

Vaccinations and Future Vaccinations

Human Papilloma Virus vaccines stimulate the body to produce antibodies that will bind to the virus, protecting the targeted host cells. The current HPV vaccines are based on virus-like particles (VLPs) that are formed by HPV surface components. VLPs are not infectious because they lack the DNA of the virus. However, they closely resemble the natural virus, and antibodies against the VLPs also have activity against the natural virus. VLPs are strongly immunogenic, which means they induce elevated levels of antibody

production by the body (NIH, 2024). This makes the vaccines highly effective. After twelve years of monitoring the safety of HPV vaccines, there are no side effects besides soreness on the arm from injection. The only issue documented has been fainting after an injection but nothing serious or life threatening. There are two vaccinations available for females and only one available for males. Research is continuously being conducted for more vaccinations especially for males. Moffitt Cancer Center has been working for over a decade to better understand HPV infection, especially in men. They are testing a study vaccine to evaluate how the body handles the vaccine. It is a phase three trial among healthy unvaccinated men ages twenty to forty-five to prevent persistent oral HPV infection (Moffitt Cancer Center, 2024). If approved, this would be the second vaccine available for men and the third for women.

Conclusions

I believe the information given in these articles supports the data of my topic. After gathering research over many years and across the globe, there is somewhat of an understanding of Human Papilloma Virus in males. There is still more research to be done and questions to be answered. For example, I wonder if more research were conducted in lower income countries if the numbers would increase. I can hypothesize that if research were completed on the same places and ages of men who were unvaccinated versus vaccinated, the numbers would skyrocket. These articles help show that getting the vaccination at an age before your first sexual encounter lowers the risk of developing cancer from an HPV infection regardless of gender. Unfortunately, there is little research on this topic for both men and women, but the researchers grabbed all the possible research they could and developed an adequate amount of data. We need to continue to research this topic, because with more research comes more knowledge and more power.

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