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Human Papillomavirus and Cancer in Men

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Abstract

Although human papillomavirus (HPV) issues have focused primarily on females, it is important to give attention to males because the primary mode of transmission of the virus is through sexual intercourse. There is increasing evidence that HPV is causing serious diseases like penile, anal, head, and neck cancer among males. Studies have also shown that, generally, males have similar rates of HPV infection (0.29 to 0.39 per 1000 person-month) as females. The vaccine against HPV, Gardasil[®], has been used in women since 2006. In 2009, the FDA approved Gardasil[®] for men. Although questions about the efficacy of HPV vaccination in males remain, it is important to understand what males know about HPV and their predisposition towards being vaccinated against the virus.

Keywords: Human papillomavirus; Virus; Cancer; Penile; Anal; Oropharyngeal

HPV and Cancer

The primary goal of clinical management is to identify and treat high-grade HPV-related infections in order to diminish the risk of developing invasive cancer. Persistent infections with high-risk HPVs cause almost all cervical cancers and many vulvar, vaginal, penile, and anal cancers in both men and women [1,2]. The most recent World Health Organization/International Agency for Research Cancer (WHO/IARC) Summary Report [1] revealed that HPV types 16 and 18 were found in nearly all cases of HPV-related cancers. The report included evidence that the following HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) were increasingly associated with cancers caused by the virus. HPV type 33 was of particular interest as it has been linked with cancer of the vulva, as well as anal cancer in both males and females [1]. Recent data from the National Cancer Institute revealed that HPV was the underlying cause of roughly 5% of all cancers worldwide [3].

Even though there is variability in the exact number of HPV-related cancers in the United States each year, the data

confirm the virus is linked to most cancers of the genital region. Multiple studies have shown that HPV contributed to anal (90%-93%), oropharyngeal (12%-63%), penile (36%-46.9%), vaginal (40%-64%) and vulvar cancers (40%-51%) [4-8].

Figure 1 illustrates the annual rates of HPV DNA found in cancer for each anatomical site. With the increasing prevalence of HPV-related infections and subsequent diseases, researchers with the CDC conducted a study examining the most recent cancer data in the United States [9]. The authors of the report noted that "population-based cancer registries are important surveillance tools to measure the impact of cancer rates on public health interventions such as vaccination and screening" [9]. The goal was to identify the role of HPV in the reported cases of cancer between 2004-2008. The most prominent cancer registries in the nation were used to obtain data for cancers of the cervix, vulva, vagina, penis, anus, and oropharynx [9,10].

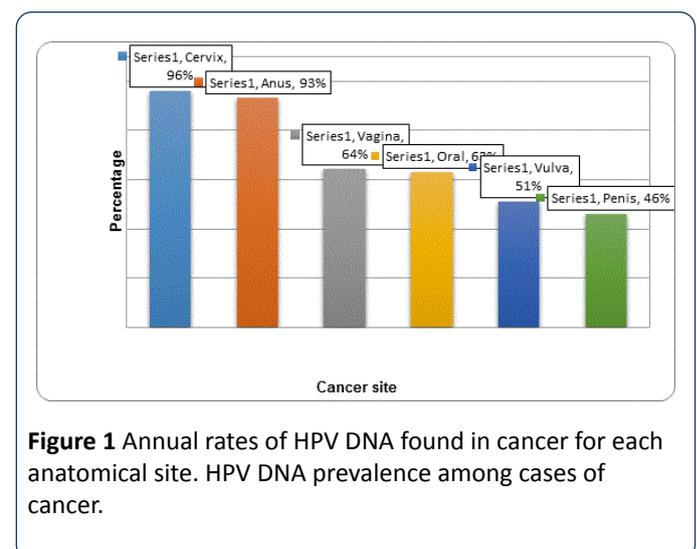


Figure 1 Annual rates of HPV DNA found in cancer for each anatomical site. HPV DNA prevalence among cases of cancer.

The results revealed that an average of 33,369 HPV-associated cancers were diagnosed annually, of which 21,290 were females and 12,080 were males [10]. The highest number of cancers related to HPV was among women, with 96% of all cervical cancers caused by the virus. A total of 4,767 cases of anal cancer were reported between 2004-2008, with the results indicating that 93% (n=4,500) were attributed to

HPV. Oral cancers linked to HPV were relatively high, with 63% of all estimated cases each year caused by the virus. The report noted other contributing factors to oral cancer included factors like smoking or alcohol consumption [10].

The researchers revealed that a total of 3,136 cases of vulvar cancer were reported per year, yet only 51% (n=1,600) were found to be HPV-related. A 2012 study indicated that the low number may be due to limited empirical studies reporting the number of vulvar cancers each year; the researchers found that 46% of the annual cases of penile cancers were attributed to HPV [11]. While penile cancer rates are overall low in the United States, it is unclear exactly what role HPV has with this cancer. More data and published studies were recommended for nearly all of the non-cervical HPV-related cancers, as the longitudinal data does not exist like it does for cancers of the cervix [9].

Regarding age, the CDC [9] indicated that, "Cervical cancer is usually diagnosed at younger ages than other HPV-associated cancers...with anal and oropharyngeal cancers generally diagnosed at slightly younger ages in men than in women". The CDC data [9] revealed that the median age for diagnosis of HPV-related cancers (which is the middle age at which 50% of all patients are either younger or older) was:

- 48 years for HPV-associated cervical cancer.
- 66 for HPV-associated vulvar cancer.
- 69 for HPV-associated vaginal cancer.
- 68 for HPV-associated penile cancer.
- 60 among women and 56 among men for HPV-associated anal cancer.
- 61 among women and 58 among men for HPV-associated oropharyngeal cancers.

The median age for anal cancer in women was 60 years old, with men slightly lower being diagnosed at 56 years of age. Cancer of the oropharynx was notably different between men and women, with the median age for men being 58 years old and 69 years of age for women. Each type of cancer had varying rates for the assigned age groups, with the results presented in Table 1. Women between 30-39 years old had the highest number of HPV-related cancers compared to any other types of cancer for people this age. The majority of cancers showed a notable increase around the age of 50, with women over the age of 80 years representing the highest rates of vulvar cancer (24.9%) [9].

The Centers for Disease Control and Prevention [9] noted that the results of this analysis determined that an estimated average of 21,290 HPV-associated cancers occurred among females each year during 2004–2008, making these cancers combined more common than ovarian cancers and nearly as common as melanoma among females. The combined burden among men was smaller, with an average of 12,080 cases per year, roughly equivalent to the number of invasive brain cancers occurring annually among men.

HPV-Related Cancer and Men

One of the primary challenges associated with HPV-related diseases in men is their latency, as they may be infected with the virus without any overt symptoms or signs [12]. Palefsky [12] maintains that without any outward signs of disease or infection, patients delay treatment, posing a challenge for providing a proper diagnosis. Adding to the complexity of this situation is that penile and anal cancers are relatively rare in North America [12]. As a result of this, symptoms that do develop because of HPV may not be immediately identified as such [12].

Table 1 Estimated annual cases of HPV-related cancers in the U.S. by age group: 2004-2008 [14].

Age Group	Cervical	Oral	Anal	Vulvar	Penile	Vaginal
0-19	15	0	0	0	0	0
20-29	650	24	12	17	5	0
30-39	2,525	209	182	144	33	21
40-49	3,000	1,831	933	461	97	74
50-59	2,411	4,209	1383	573	182	132
60-69	1,589	3,184	1018	536	261	147
70-79	975	1,656	735	623	262	167
>80	602	613	503	781	205	184
Total	11,767	11,726	4,766	3,135	1,045	725

On top of the challenges regarding the detection, diagnosis and treatment of HPV infection and related diseases in men, a 2009 study [13] noted that prevalence rates of HPV-related cancers do not provide the impetus for researchers to seek additional insight into the disease. For example, the CDC [14] reported:

Cancers of the penis, anus and oropharynx are uncommon, and only a subset of these cancers are actually related to HPV, [yet] each year in the United States there are about:

- 400 men who get HPV-related cancer of the penis,
- 1,500 men who get HPV-related cancer of the anus,
- 5,600 men who get cancers of the oropharynx (back of throat), but many of these cancers are related to tobacco and alcohol use, not HPV.

Anal cancer: According to researchers at the University of California–San Francisco (UCSF) [15], anal cancer is similar to cancer of the cervix. The principal cause of anal cancer is human papillomavirus (HPV), a common virus that causes changes in the skin. Anal HPV infection is most commonly acquired through anal intercourse, but it can also be acquired from other genital areas that are infected, particularly from the vulva in women, or from the penis in men.

The NCI [3] recently revealed that roughly 85% of all cases of anal cancer are caused by high-risk HPV 16, with types 16

and 18 the most common cause of HPV-related anal cancer. This is notable as these same two high-risk types (16 and 18) account for roughly 70% of all cervical cancers [16]. According to the ACS [16], risk factors for anal cancer include:

- Being infected with human papillomavirus (HPV)
- Being over 50
- Having multiple sexual partners
- Engaging in anal intercourse
- Frequent anal redness or soreness

The incidence of anal cancer is approximately 1.5/100,000 in the general population [17,18], with Palefsky et al. [19] reporting that, "the incidence is increasing by approximately 2% per year among both men and women in the general population". Men who have sex with men (MSM) are roughly 17 times more likely to develop anal cancer [14], with Palefsky et al. [19] reporting that other high risk groups included, "men and women infected with the human immunodeficiency virus (HIV), women with cervical or vulvar cancer, and persons receiving immunosuppressive treatment to prevent solid organ graft rejection".

Misdiagnosis of anal cancer is common, as the CDC [14] indicated that sometimes there are no signs or symptoms, [or there may be]:

- Anal bleeding, pain, itching, or discharge
- Swollen lymph nodes in the anal or groin area
- Changes in bowel habits or the shape of your stool

Presently, much of the information about anal cancer was derived from what is known about cervical cancer. This is due, in part, to the similarities between the types of the tissues involved in these two areas [20]. Just as cervical cancer is preceded by high-grade cervical intraepithelial neoplasia (CIN 2 or 3), anal cancer is preceded by high-grade anal intraepithelial neoplasia (AIN 2 or 3) [21,22]. While research is limited confirming the progression of an AIN 2-3 lesion to anal cancer, patients with these advanced infections are considered at high risk of developing cancer due to the similarity with lesions in the cervix [22].

Anal cancer is often missed or misdiagnosed, many times, as hemorrhoids. According to UCSF's [3] anal cancer website, the possibility of cancer is often overlooked and symptomatic patients are told that they are suffering from hemorrhoids and are not examined with a simple digital anorectal exam (DARE). A DARE exam is conducted when a health professional examines the anus and rectum for abnormalities indicating signs of cancer. De Sousa and Duraes [20] indicated this exam is useful as "The lesions would be palpable, even in the absence of clinical symptoms". However, this test is rarely used even though it is the least expensive [20].

To date there have been limited clinical trials carried out to validate the effectiveness of any type of screening process for anal cancer [23]. According to Darragh and Winkler [23], the "clinical approaches to the diagnosis of anal intraepithelial neoplasia (AIN) borrow from the cervical cancer model and include the application of colposcopy to evaluate the anal canal and perianal region". The Pap smear has been

established as an effective way to detect cervical dysplasia and has decreased the rates of cervical cancer in women worldwide. Taking into account the similarity between anal and cervical cancer, there are proposals for comparable population screenings to detect anal cancer [23]. De Sousa and Duraes [20] noted that the adoption of such programs "is limited by little evidence that such interventions alter the natural history of HPV infection and progression to anal cancer" that is only worsened by the lack of empirical studies necessary to validate a particular method.

While no official recommendations exist regarding anal cancer screening, more and more doctors are employing tests modeled after the Pap testing and cytology. Like the Pap smear, the anal cells are examined by a pathologist to identify abnormalities or dysplasia, that if present are examined further to identify the nature of infection in the anus and lower rectum [23]. The abnormalities discovered through the anal cytology are followed by a high-resolution anoscopy (HRA), with a biopsy taken when an abnormality is confirmed.

The problem lies with limited experience in interpreting the anal cell samples, as anal cytology is relatively new to the field of pathology [23]. Moreover, this process requires specific training and equipment that few primary care clinicians have undergone, even though the techniques and tools have been part of most obstetrical, gynecological, colorectal, surgical, and gastrointestinal practices, and training programs [23].

Goldstone [24] reported that if we are to assume that anal dysplasia is similar to cervical dysplasia in its natural history and pathogenesis, compounded by the seemingly high prevalence and incidence of HSIL [AIN 2/3] in certain populations, the suggestion that anal cytology screenings may play an invaluable role in detecting high grade dysplastic lesions is merited.

Goldstone [24] added that groups who should be considered for screening include: women with cervical cancer or high-grade vulvar disease/cancer; all HIV-positive men and women, regardless of sexual orientation; individuals with perianal condylomaacuminata; and other immune-compromised individuals such as transplant recipients.

Treatment for anal cancer is determined by many factors that include the location, type and stage of cancerous tumor in the anus. Additional considerations are the individual's age and overall health with the final decision determined between patients and their physician [23]. Goldstone added that "If anal intraepithelial neoplasia is the anal squamous-cell carcinoma precursor...[surgically removing AIN 2/3] will hopefully will prevent progression to cancer".

Penile cancer: A 2009 study evaluated the development of HPV infection that results in cancer in both women and men noting the following observations: "The incidence of penile cancer is lower compared to that of cervical cancer, likely due to the lower susceptibility of the penis to malignant transformation as compared to the cervix" [25]. The researchers [25] reported that research regarding penile cancer has not considered the specific etiology of the disease. In short, research offers less information about the genesis

and development of penile cancer when compared with cervical cancer.

Palefsky [12] revealed that, "Unlike sampling a moist surface such as the cervix, reliable sampling of the dry, keratinized surface of the penis to obtain adequate numbers of cells has been difficult and poorly reproducible". Palefsky [12] also noted that once penile cancer has developed, challenges exist with regard to diagnosing the lesions that develop, as there are currently no standardized methods for testing for HPV-related cancers in men.

The data on penile cancer indicates that the disease is most commonly found in older men over the age of 60 [13]. While the disease is sometimes reported in young men, Bleeker et al. [13] asserted that the rates of penile cancer in this group have remained relatively stable over time and have even declined in the United States over the last several years. Bleeker et al. [13] revealed that in the United States, "age-standardized incidence rates range from 0.3 to 1.0 per 100,000, accounting for 0.4–0.6% of all malignancies in this part of the world".

Although HPV-related penile cancer is rare in the United States, the rate of disease is much higher in developing nations. Bleeker et al. [13] found that, "The disease can constitute up to 10% of malignant disease in men in some African, Asian, and South American countries, with incidence rates of 4.2 and 4.4 per 100,000 in Paraguay and Uganda, respectively." Bleeker et al. [13] added that "penile cancer is predominantly seen in men who have not been circumcised shortly after birth, and is very rare in populations who routinely practice circumcision during the neonatal or childhood period". Poor hygiene is also a predominant risk factor for the development of HPV-related infections and diseases. Palefsky [26] also reported that, "The incidence of penile cancer is low relative to cervical cancer, particularly in developed countries. This may, in part, reflect different rates of circumcision, which is known to be a protective factor for penile cancer".

Treatment of penile cancer may be invasive and painful for the patient with the least harm caused when cancer is early (stage I) and local excision of the tumor is possible [12]. Palefsky [12] noted, however, that in later stages of the disease treatment may include: "penectomy, lymph node removal on both sides of the groin, radiation therapy and chemotherapy may be required".

HPV in Men

With a basic review of HPV in women provided, it is now possible to look more closely at HPV infection in males. Research regarding HPV infections in males suggests that the etiology and pathophysiology of the infection in males is much different than it is in females. A 2009 study evaluated the development of HPV infection that results in cancer in both women and men noting the following observations: "The incidence of penile cancer is lower compared to that of cervical cancer, likely due to the lower susceptibility of the penis to malignant transformation as compared to the cervix" [25]. The researchers go on to report that research regarding

penile cancer has not considered the specific etiology of the disease [25]. In short, research offers less information about the genesis and development of penile cancer when compared with cervical cancer.

Likewise, a 2007 study also reviewed the challenges associated with understanding the etiology and pathophysiology of HPV infection and HPV-related diseases in men [12]. As reported by this author, the challenges associated with studying HPV infection and related diseases in men are unique and restrict the ability of researchers to fully examine disease progression. One reason may be that it is difficult to obtain an adequate number of cells from the surface of the penis [12]. This researcher also noted that once penile cancer has developed, challenges exist with regard to diagnosing the lesions that develop, and there are currently no standardized methods for testing for HPV-related cancers in men [12].

Other challenges associated with HPV-related cancers in men include their latency. In many instances, HPV-related diseases will be present in men without any overt symptoms or signs [12]. Palefsky [12] maintains that without any outward signs of disease or infection, patients delay treatment posing a challenge for providing a proper diagnosis of the patient. Adding to the complexity of this situation is that penile and anal cancers are relatively rare in North America [12]. As a result of this, symptoms that do develop because of HPV-infection or related cancer may not be immediately identified as such [12]. Treatment of HPV-related cancers in the genitals can be invasive and painful for the patient [12]. For example, in later stages, removal of the penis or lymph nodes or even radiation or chemotherapy may be necessary [12].

In addition to the challenges reported with detection, diagnosis and treatment of HPV infection and related diseases in men, Bleeker et al. [13] noted that prevalence rates of HPV-related cancers do not provide the impetus for researchers to seek additional insight into the disease. Research regarding penile cancer indicated that the disease is most commonly found in elderly men over the age of 60. While the disease is sometimes reported in young men, Bleeker et al. [13] asserted that the rates of penile cancer in this group have remained relatively stable over time and have even declined in the United States over the last several years. In the United States, "age-standardized incidence rates range from 0.3 to 1.0 per 100,000, accounting for 0.4–0.6% of all malignancies in this part of the world" [13].

HPV-related diseases in men

The statistical association between HPV and its relationship to cancers in men is provided in Table 2. It is evident that these statistics run almost parallel to the statistics of cervical cancer cases that occur in women in the United States annually. These facts alone change the perception that only women are at risk from HPV.

Mouth and throat cancers are linked to oral sex. Despite the correlation between the decline in the rates of cigarette smoking after the 1960s and the reduction in the overall rates of head and neck cancers, the rates of throat cancers,

particularly those of the tonsils, base of the tongue and back of the throat did not decline and actually appeared to be gradually rising. The missing link was eventually found in HPV infections, specifically infections caused by HPV16 strain, which partially negated the overall reduction in head and neck cancers that was gained from the decline in tobacco use.

Table 2 Approximate number of new cases of HPV-related diseases in US males annually [16].

Diseases	# of new cases/year	% with detectable HPV	Number of new HPV-related cases
Recurrent respiratory papillomatosis	Approximately 3,300	100%	All 3,300/year
Genital warts	Approximately 500,000	100%	All 500,000 cases/year
Cancer of mouth and throat (Head and neck cancers)	25,830	27%	6,948/year
Anal cancers	1,910	90%	1,719/year
Penile cancers	1,530	50%	765/year
Total number of new HPV-related cancers			9,432/year

HPV vaccination in men

Not surprisingly, the development of the HPV vaccine for women prompted debate over whether or not young men should receive the same vaccine [27]. Kim [27] provided an overview of data regarding HPV and related cancers in men and women, noting that HPV infections contribute to 20,000 cases of invasive cancer in the United States annually. Of these cancers, less than 25% occur in men. Kim [27] asserted that while 99.7% of cervical cancers in women can be attributed to HPV infection only, about 90% of anal cancers stem from HPV infection. Smaller portions of remaining cancers (penile, neck and head) may be attributable to HPV infection. Given that there is a specific link between HPV and penile, anal, head and neck cancers found in men, widespread HPV vaccination does not appear to receive a lot of support for this group. Kim [27] maintained that HPV-related cancers, which are more frequently reported in men who have sex with men, should prompt guidelines for the development of vaccination protocols based on risk classification for the individual.

Although Kim [27] argued that there is no real public health impetus for utilizing HPV vaccination for males, studies examining the efficacy of HPV vaccination in this group have suggested that vaccination may have some value [7]. Specifically, a 2011 randomized, placebo-controlled, double-blind study [7] evaluated the efficacy of the vaccination. The research evaluated use of the HPV vaccine to reduce genital lesions in boys and men and included 4,065 male subjects between the ages of 16 and 26 years from 18 different countries [7]. The results of the investigation demonstrated that 36 external genital lesions were seen in the vaccine group as compared with 89 in the placebo group, for an observed efficacy of 60.2%. Based on these findings, the authors

concluded that the vaccine could be effective for reducing genital warts caused by HPV infections in men [7].

Furthermore, research from 2008 suggested that the immunization of males against HPV would be cost effective for preventing the spread of the infection in females and the subsequent development of cervical cancer [28]. Despite this potential, there is a paucity of support for making HPV vaccination mandatory for men [28]. "It appears that HPV vaccination would remain a gender specific requirement for immunization, despite potential advantages to women if men were also immunized" [28].

Other scholars examining the issue of vaccinating males against HPV have made similar observations to those reported in earlier research [29]. Specifically, Hollander [29] noted a study in which physicians were surveyed about HPV vaccination of males. A majority of physicians surveyed believed that HPV vaccination should be made available for males arguing that "vaccinating males would be important not only because it would prevent disease in males, but also as a strategy for protecting females from the risk of HPV infection and its consequences". Hollander [29] continued to report that there was little support for the idea that female vaccination for HPV negated the need for males to be vaccinated as well. Most physicians surveyed (96) believed that policies regarding HPV vaccination should be gender neutral to provide a comprehensive approach to combating HPV infections and related diseases [29].

Scholars examining HPV vaccination of males also have focused on the general social and public health benefits that could be achieved through male vaccination [30]. According to Hull and Caplan [30], the basic tenets of herd theory and immunity suggest that the best means for controlling the spread of a disease is by providing wide-scale population intervention. This includes vaccination of both males and females to prevent and restrict the spread of disease. Although this theory continues to dominate the development of vaccination protocols in the United States, Hull and Caplan [30] noted that with regard to HPV vaccination, this has not been the case. Initial efforts to increase HPV vaccination have focused primarily on women because "they bear the bulk of disease burden". Continued use of HPV vaccination in this manner is unethical and, according to Hull and Caplan [30], would continue to perpetuate gender inequalities in healthcare.

Conclusion

It has further been studied and shown that the rate of HPV infection in men, when compared to women, is more constant among men in all age groups. In women, the highest rates of infection are seen in their twenties, with rates then decreasing in their thirties and surging again in their forties and fifties, either due to reactivation of dormant infections or reinfection from men. Presently, there are not many studies that exist between the association of men and HPV-related diseases, but there are numerous theories and myths about HPV and men. Scientific research developed so far has helped our society

better understand the overall prevalence rates of HPV and cancer in men.

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