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The Necessity of Human Papillomavirus Vaccination in Men: A Narrative Review

Sooyoun Kim[1], Sangrak Bae[2]

[1]Institute of Health and Environment, Seoul National University, Seoul, Korea
[2]Department of Urology, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

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Corresponding author:
Sangrak Bae
Department of Urology, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 271 Cheonbo-ro, Uijeongbu 11765, Korea
Email: robinbae97@catholic.ac.kr
https://orcid.org/0000-0002-8364-704X

Anogenital wart caused by human papillomavirus (HPV) is the most common sexually transmitted infection. High-risk strains, such as types 16 and 18, cause penile cancer in men, cervical and vulvar cancers in women, and head and neck cancers and anal cancer in both sexes. Since these malignant tumors can be prevented through vaccination, the importance of vaccination is emphasized. However, because HPV is known to cause cervical cancer, vaccination is only being administered to women. Some countries vaccinate men as well, but in South Korea, only girls are included in the National Immunization Program. However, screening for HPV in men is not possible, and the virus causes various malignant tumors, with a sharp increase in head and neck cancers, as well as a surge in genital warts in the country. In addition, HPV worsens sperm quality. Moreover, the need for vaccines is increasing as the known methods for preventing HPV-related diseases in men are decreasing and the disease burden is increasing. As cost-effectiveness studies have shown that the cost-effectiveness of vaccination is lower for men than for women, it is unlikely that male vaccination will be included in national immunization programs. Many countries overseas, especially a very small number of OECD (Organization for Economic Cooperation and Development) countries including South Korea, are implementing mandatory vaccination for women. Vaccinating men and women, would be cost-effective and efficient in achieving herd immunity. In addition to herd immunity, the inclusion of male vaccination in the National Immunization Program is imperative given the rapidly increasing incidence of diseases in men.

Keywords: Human papillomavirus, Vaccination, Uterine cervical neoplasms, Oropharyngeal neoplasms, Condyloma acuminata

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HIGHLIGHTS

Men are also affected by various human papillomavirus (HPV)-related diseases, and the incidence of HPV-associated malignancies in men is on the rise. However, there are no appropriate screening tests available for men. Including men in the HPV vaccination program is also an efficient way to achieve herd immunity. HPV infection is known to reduce sperm quality, and the rate of circumcision, which has been suggested to help prevent HPV infection, is decreasing. Just as HPV-related diseases are prevented in women through vaccination, it is essential to include men in the national vaccination program as well. Additionally, catch-up vaccination should be implemented by expanding the age range for vaccination eligibility.

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INTRODUCTION

Human papillomavirus (HPV) can appear in anyone who is sexually active. In most cases, people become infected but show no symptoms or develop any diseases. The virus often remains in the body but naturally disappears in about 90% of cases [1]. However, in some instances where the infection persists in the body, it can penetrate tissues and lead to malignant tumors [2]. It is known that many of the malignant tumors caused by HPV can be largely prevented through vaccination. However, achieving herd immunity against HPV involves many challenges, such as reaching high vaccination rates and ensuring vaccination for both men and women without distinction [3-6]. Many countries around the world, especially OECD (Organization for Economic Cooperation and Development) countries, have implemented HPV vaccination as part of their national immunization programs for men as well [7-9]. However, in South Korea, the National Immunization Program currently targets only girls and some low-income women. In order to achieve herd immunity, a certain level of vaccination coverage must be reached. This discussion seeks to explore, from various perspectives, why HPV vaccination is also necessary for men.

WHAT IS HPV?

HPV belongs to the family Papillomaviridae and is a nonenveloped, double-stranded DNA virus [10]. There are over 200 species of HPV, and about 30 to 40 types cause diseases in the genital and anal regions [11]. HPV mainly invades epithelial cells and mucous layers, has a long incubation period, and can remain in the body for a long time. In most cases, it is confined to the infected area and remains asymptomatic, often disappearing naturally after about 18 months without special treatment [12]. However, in some cases, the virus persists in the body or penetrates deeper into tissues, causing diseases [13]. HPV types are classified into high-risk and low-risk groups, with about 20 types categorized as high-risk, causing malignant tumors, including types 16 and 18 (Table 1). Low-risk types, such as types 6 and 11, cause diseases like genital warts. When classified by gender, it causes head and neck cancer, anal cancer, and genital warts in both men and women, cervical cancer and vulvar cancer in women, and penile cancer in men.

Table 1. Classification of human papillomavirus viruses according to risk of malignancy

Group	Subtype
Low risk	6, 11, 32, 40, 42, 43, 44, 54, 55, 61, 62, 67, 70, 72, 81
High risk	16, 18, 31, 33, 45, 52, 58, 26, 35, 39, 51, 53, 56, 59, 66, 68, 69, 73, 82

Initially, attention was drawn due to its close association with cervical cancer in women, and the concept of being a preventable cancer through vaccination led to a Nobel Prize and garnered global interest in terms of women's health rights, with many countries actively engaging in efforts [14]. In 2018, the World Health Organization made the following statement, urging the world to participate in combating HPV-related diseases and emphasizing the importance of prevention through vaccination.

In 2018, it was reported that approximately 30 million cases of genital warts occurred worldwide, along with 530,000 cases of cervical cancer, 20,000 cases of female genital tumors, 38,000 cases of head and neck cancer, 13,000 cases of penile cancer, and 35,000 cases of anal cancer [15-19]. These conditions are transmitted through sexual activity and primarily cause cervical cancer in women. Currently, in most countries, vaccination is provided for women under the assumption that the health risks for women are significant. However, many countries are also vaccinating men, as they have determined that vaccinating men contributes to disease eradication, achieving herd immunity, and that gender-neutral vaccination is cost-effective.

When looking at the rate of transmission through sexual intercourse, the rate from women to men is confirmed to be higher than from men to women [20]. Although this is due to differences in anatomical structure

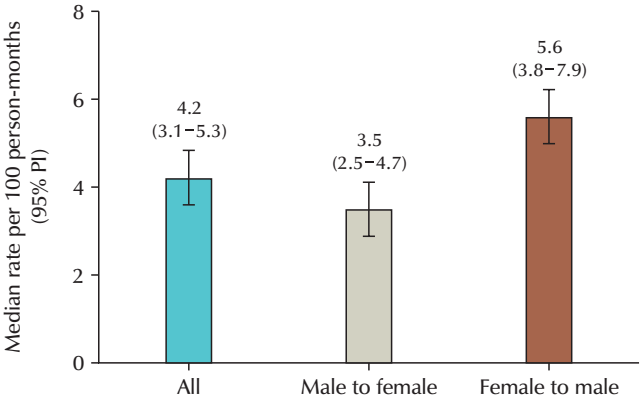

Fig. 1. Transmission rate of human papillomavirus infection between heterosexual couples. PI, posterior interval.

and the possibility of the virus remaining in the human body, the transmission rate from men to women is also not small, so vaccination only for women is limited (Fig. 1). After all, women are transmitted from men.

CURRENT STATUS OF HPV VACCINATION IN KOREA

In 2006, the quadrivalent vaccine Gardasil was approved by the U.S. Food and Drug Administration (FDA), and in 2007, the bivalent HPV vaccine was launched by GSK (GlaxoSmithKline, London, UK). In Korea, the bivalent vaccine was approved in 2007 and the quadrivalent vaccine in 2008. Thanks to its clear preventive effects against cervical cancer, HPV vaccination was introduced into the National Immunization Program for girls aged 12 in 2016. However, as of January 2023, vaccination for boys has not yet begun. The nonavalent vaccine, which includes five additional types, was launched in 2016. In 2022, the vaccination age for women was expanded to include ages 13 to 17, and low-income groups were supported until age 26. The U.S. FDA also approved the vaccine for head and neck cancer in 2022, and approval in Korea is expected soon. The indications for the catch-up vaccine for women have been expanded to 45 years of age. Currently, the HPV vaccines in Korea that are indicated for males are 4-valent and 9-valent. However, men are not receiving national support regardless of age. Recently, in terms of youth health and women's health, the government and the National Assembly have legislated to include men and to vaccinate adolescents regardless of gender by the age of 12 or 17, and interest in including male vaccination is increasing as the 20th President's strategy includes male vaccination. In addition, the vaccination age has been extended to 45 years for females, while it is 26 years for males. The indications for females have been expanded to the age at which vaccination is effective, but males, who are included in the national vaccination in other countries such as Australia, have not been approved for national vaccination or have their vaccination age expanded due to insufficient research on male diseases related to HPV in Korea.

WHY IS HPV VACCINATION NECESSARY FOR MEN?

1. Men Can Also Contract Diseases Caused by HPV

Despite initially being known as the "cervical cancer virus" and "cervical cancer vaccine," HPV also affects men. The misconception that HPV only concerns women has hindered awareness of its impact on men. HPV infection also causes many diseases in men, and some diseases occur only in men or occur more often in men. HPV-related diseases in men include penile cancer, anal cancer, and head and neck cancer, anogenital warts (Table 2).

Anogenital warts are one of the most common sexually transmitted infections and the most prevalent of HPV-related diseases. Genital warts are another common condition in men. Although penile cancer is relatively rare, it is associated with HPV, as are anal and head and neck cancers. In a study of HPV-related tumors, when HPV DNA was detected in approximately 16,000 malignant tumor specimens, anal cancer and cervical cancer showed the highest correlation at 88.3% and 84.8%, while penile cancer and head and neck cancer also showed correlation at 33% and 25%, respec-

Table 2. various diseases depending on the various types of subtypes

Disease	HPV type
Common warts	2, 7, 22
Plantar warts	1, 2, 4, 63
Flat warts	3, 10, 28
Anogenital warts	6, 11, 42, 44, and others
Anal dysplasia (lesions)	6, 16, 18, 31, 53, 58
Genital cancers	• Highest risk: 16, 18, 31, 45
	• Other high-risk: 33, 35, 39, 51, 52, 56, 58, 59
	• Probably high-risk: 26, 53, 66, 68, 73, 82
Epidermodysplasia verruciformis	More than 15 types
Focal epithelial hyperplasia (mouth)	13, 32
Mouth papillomas	6, 7, 11, 16, 32
Oropharyngeal cancer	16
Verrucous cyst	60
Laryngeal papillomatosis	6, 11

HPV, human papillomavirus.

tively [21,22].

The prevalence of HPV-related disease is rapidly increasing in Korea, particularly among men. In a study using data from the Health Insurance Review and Assessment Service (HIRA) from 2007 to 2015, while the prevalence among women showed a decreasing trend, it continued to increase steadily among men. Additionally, the associated medical costs have also shown a rising trend [23]. Subsequently, extending the period to 2018 and segmenting the data by age, the age-specific prevalence, medical costs, and the total number of patients continued to show an increasing trend [24]. The number of patients increased by approximately 350% from 2007 to 2018. Even taking into account the shortcomings of the diagnostic-based data, we can see that the treatment-related portion is also increasing rapidly in men, and that anogenital warts are increasing rapidly, centering on the increase in men overall [25].

2. Increasing Trend of Male Cancer Among HPV-Related Cancers

Approximately 5% of all cancers worldwide, around 730,000 cases, are related to HPV. Traditionally, cervical cancer has been the most representative tumor caused by HPV. Even today, in developing countries, cervical cancer remains the most significant HPV-related malignancy. This led to the prevalent notion that HPV is primarily a concern for women. However, HPV not only affects women but also causes malignant tumors in men, including penile cancer, head and neck cancer, and anal cancer. In particular, oropharyngeal cancer (a type of head and neck cancer) is more common in men, occurring four times more often than in women, and now exceeds cervical cancer cases [26]. Among head and neck cancers, there are malignant tumors unrelated to smoking that are associated with HPV. A Canadian study found that men develop head and neck cancer about 2.5 times more often than women [27]. In the United States, the incidence of these HPV-related malignancies has steadily increased among men, surpassing the incidence of cervical cancer in women [26]. Head and neck cancers are known to be closely linked to oral sex. This trend has also been observed in Korea, where population-based studies show a sharp increase in head and neck cancer cases among men [28]. Using the big data from the HIRA, the incidence of head and neck cancer in the country has been shown to be significantly higher in men compared to women (Fig. 2).

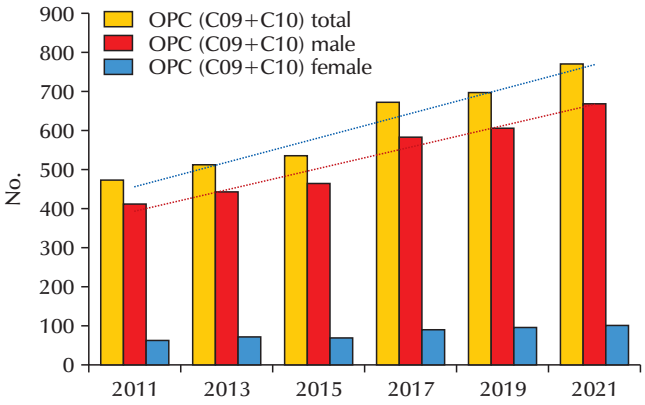

Fig. 2. Incidence of oropharyngeal cancer (OPC) in Korea (Health Insurance Review and Assessment Service Big data service).

Penile cancer occurs mainly in people aged 50 to 70 and is closely related to HPV, of which type 16 is the

most commonly found, followed by type 18 [29,30]. In the case of penile cancer, it is known that about 33% are related to HPV. Looking more closely, penile high-grade squamous intraepithelial neoplasia shows an HPV positivity rate of over 80%, and in the case of invasive penile cancer, it shows a correlation of 32%–35% [22]. In Korea, the number of new cases of penile cancer increased by about 35% from 55 in 1999 to 74 in 2020. However, as can be seen from the number of patients, it is a very rare cancer. However, the number of patients showed an increasing trend [31].

3. Absence of Screening for Men

HPV infection is a state of virus retention, that is, a state of virus retention that does not cause disease, and there is a difference between the silent infection and the disease, and the virus exists in the body for a long time, about 10 years or more, and then invades the tissue and causes malignant tumors such as cervical cancer. However, in the case of men, most of the virus naturally disappears or is cleared after up to 18 months, so there is a discrepancy between the disease and the infection state. Cervical cancer can be detected early through a screening test called the Pap smear, but there are no equivalent screening methods for penile, anal, or oropharyngeal cancers. Swab tests on male genital skin have low sensitivity and are therefore unreliable [32]. Additionally, it is not appropriate as a screening test because it appears differently depending on the location of the lesion or the shape of the sampling tool [33]. Urine samples have a lower diagnostic rate in men than in women [34]. Screening tests using oral samples also show similar patterns [35]. Due to the anatomical structure of these areas, detecting the virus through smear or swab tests is difficult. However, recently, first-voided urine and oral swabs are also being considered as alternative methods [36]. However, it does not yet reach the same level of accuracy as the screening test for women. Regular check-ups and vaccination remain the best ways to prevent these cancers in men.

A recent domestic study reported that approximately 60% of healthy adult men carry the virus [37]. It was confirmed that even healthy men have a very high probability of having HPV as a silent infection or carrier. Therefore, they act as transmitters to women, and vaccination for prevention is necessary for transmitters as well. However, the study stated that 35% of the viruses could not be prevented by the 9-valent vaccine, requiring additional measures.

4. Achieving Herd Immunity

HPV vaccination started as a means of preventing cervical cancer in women, but now, about 140 countries are vaccinating women, 62 countries include men in their national vaccination programs. Many countries that implement gender-neutral vaccination are trying to increase vaccination rates to eliminate cervical cancer. Achieving full coverage of HPV-related disease requires high vaccination rates and gender-neutral vaccination [38,39]. However, more effort is needed to raise vaccination rates among both men and women in Korea.

In terms of vaccination rates, the gap in the HPV prevention "blind spot" for men in Korea is widening. According to the Korea Disease Control and Prevention Agency's vaccination registration database, the HPV vaccination rate for women in Korea ranges from 62.7% to 89.7%, depending on birth year. However, the highest vaccination rate among men, those born between 1983 and 1994, was only 2.1%. In contrast, Australia, which adopted gender-neutral HPV vaccination in 2013, has declared its goal to eliminate cervical cancer within 10 years. As of 2020, the HPV vaccination rate for men in Australia was nearly 83.4%. In the United Kingdom, which began supporting HPV vaccination for both men and women in 2018, the male vaccination rate was reported to be between 60% and 70% for 2022–2023.

The World Health Organization aims to vaccinate more than 90% of women [40]. While simply increasing vaccination rates would help eradicate the disease, the real issue is cost-effectiveness. Cost-effectiveness is often considered in terms of vaccination rates by country. Korea has announced research results showing that it is

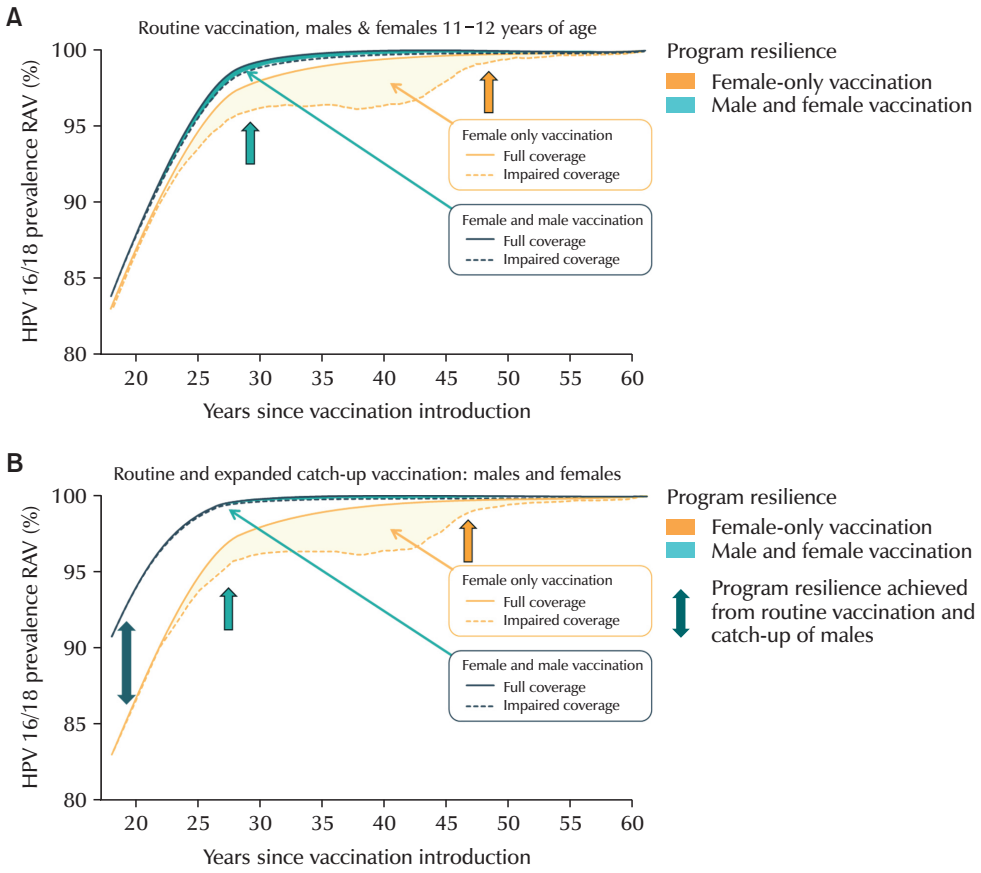

Fig. 3. Comparison of gender-neutral vaccination and gender-neutral vaccination with catch-up vaccination. (A) Gender-neutral vaccination. (B) Gender-neutral vaccination with catch-up vaccination.

more cost-effective to vaccinate only girls or to conduct catch-up vaccination for the 9-valent vaccine [41]. In overseas studies, gender-neutral vaccination was shown to be cost-effective only in Italy for males vaccinated with the 9-valent vaccine [42]. However, it is said that gender-neutral vaccination can be achieved more quickly in terms of coverage of HPV disease (Fig. 3A and B) [38].

5. Urologic Consideration

One of the most effective measures for preventing HPV in men is vaccination. Additionally, circumcision, specifically the ring incision procedure performed in urology, is also known to help in prevention [43-45]. There may be controversy about the effect of circumcision on HPV prevention and disease [43]. In a systematic review of the literature, the annular incision has a significant effect on reducing the prevalence of HPV infection in the glans. Additionally, male circumcision can reduce the risk of several sexually transmitted diseases, improve genital hygiene, prevent malignant genital tumors, and lower the transmission rate of human immunodeficiency virus/HPV [44]. Circumcision reduces the incidence of HPV and improves clearance (the time it takes for HPV to disappear from the body) [45]. It is also effective in reducing the incidence of HPV in the glans, but has a minimal preventive effect on the shaft or other areas. It also reduces the incidence of infection in female partners [46].

HPV infection affects sperm quality [47-51]. Research has shown that HPV infection in sperm decreases sperm motility and fertility, while the presence of anti-sperm antibodies increases, reducing natural pregnancy rates. When HPV infection was confirmed in semen,

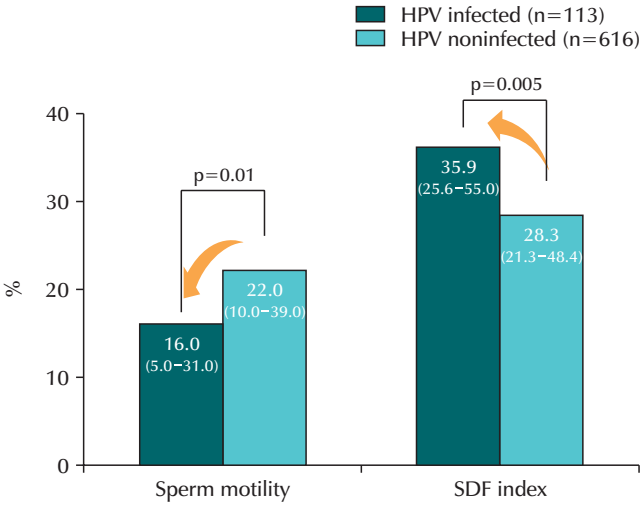

Fig. 4. Sperm motility and sperm DNA fragmentation according to human papillomavirus (HPV) infection. In HPV-infected men, sperm motility was significantly decreased and sperm DNA fragmentation (SDF) was significantly increased compared to men not infected with HPV. Values are median (interquartile range).

sperm motility was significantly reduced compared to the noninfected group [49]. A systematic review found that sperm motility was significantly reduced in men infected with HPV compared to men who were not infected with HPV [47]. Another study confirmed that in the HPV infection group, sperm motility was reduced and sperm DNA fragmentation index increased, which increased the degree of sperm gene destruction (Fig. 4) [48].

There was a study that found that the vaccine helped increase male fertility. In men with infertility, a group that received three vaccinations and a group that was observed without vaccination were compared in men who were confirmed to have HPV infection through a semen test. A study found a significant increase in normal births among vaccinated men compared to non-vaccinated men (5.5% vs. 36.7%) [50]. However, since most men facing infertility are over the age of 30, further research in Korea is needed to expand vaccination indications beyond the current age limit of 26.

CONCLUSIONS

Diseases caused by HPV are not limited to women. Recently, HPV-related diseases such as head and neck cancer and anogenital warts have been reported to occur more frequently in men than in women. However, there are no recommended screening tests for men, and there is a conceptual disconnect between viral carriage and disease development. As a result, the burden of HPV infection in men is underestimated. While women benefit from national mandatory vaccination programs that help prevent HPV-related diseases, men do not have the same access to such preventive measures. Achieving herd immunity and preventing HPV-related diseases in men requires a greater emphasis on vaccinating males as well. Both the public and the government need to address the necessity of including men in the national vaccination program, expanding the age limit for male vaccination to improve public health.

NOTES

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• **ORCID**

Sooyoun Kim: 0000-0001-5628-7985

Sangrak Bae: 0000-0002-8364-704X

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