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Human Papillomavirus Genotypes in the Korean Older Adult Population Running Head: HPV Genotypes in Korean Older Adults

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Abstract: In older populations, Human Papillomavirus (HPV) infections are likely to reactivate owing to immunocompromised, thereby increasing the risk of cervical and other cancers. However, research on HPV infection in older adults is limited and data on the sex- and age-specific distribution of high-risk HPV types are lacking. Thus, to increase the level of evidence on the extension of cervical cancer screening in older adult women and preventing and managing HPV infection in older adult populations, we investigated HPV positivity and co-infection rates by age and HPV type in Korean older adults. From January 2020 to July 2023, DNA extraction and real-time polymerase chain reaction were performed to determine HPV types in 1,167 individuals (84 men aged 69.8±5.05 years; 1,083 women aged 69.97±4.40 years) referred to a specialized laboratory. In both sexes, HPV positivity rates were higher in those aged 75-99 years than in those aged 65-74 years, although the difference was not statistically significant (men: $\chi^2 = 0.0333$, $p>0.05$; women: $\chi^2 = 0.5122$, $p>0.05$). High-risk HPV positivity rates were the highest for type 16 in men and type 52 in women. More single infections were observed than co-infections, although the difference was not statistically significant. For men and women aged ≥65 years, the single infection positivity rates were 32.1-21.1%, respectively, whereas co-infection positivity rates were 28.6-18.3%, respectively. Older adults require specific infection-prevention practices for healthy sexual behavior. Regular HPV infection screening is necessary for not only younger and middle-aged individuals but also older adults.

Keywords: Genotype, Human Papilloma Virus, Older Adults, Screening, Sexually Transmitted Infections

Introduction

In 2020, the World Health Organization reported approximately 604,127 (3.1%) new cases of cervical cancer among women across all age groups in 36 countries worldwide (Data visualization tools for exploring the global cancer burden in 2022, 2023). Among them, 194,195 cases of cervical cancer and 157,641 deaths occurred in women aged ≥60 years. As Human Papillomavirus (HPV) infection is the primary cause of cervical cancer (Li *et al*., 2011), close monitoring of HPV infections in older adults is essential. Although HPV infections are prevalent among younger individuals, these are typically resolved by the immune system. However, older adults are more likely to experience persistent HPV infections owing to a decline in immune system efficiency with age, thereby increasing the risk of developing cervical cancer in older adult women. The age-related weakening of immune responses reduces the ability to clear new HPV infections and increases the likelihood of the reactivation of previously acquired infections (García-Piñeres *et al*., 2006). These dynamics underscore the importance of understanding HPV prevalence and its implications in older populations. The negative effects and financial burden of HPV, a common sexually transmitted virus, on the development of cervical cancer, have been extensively examined (Watson *et al*., 2015), with extensive research focusing on HPV infections in both men and women (Rodríguez-Álvarez *et al*., 2018; Dibble *et al*., 2019).

HPV types are classified as high and low risk. High-risk HPV types, such as types 16-18, cause cervical

(Asiaf *et al*., 2014), oropharyngeal (Timbang *et al*., 2019), vaginal (Bertoli *et al*., 2020), penile (Liang *et al*., 2019) and anal (Krzowska-Firych *et al*., 2019) cancers. Meanwhile, low-risk HPV infections, such as types 6 and 11, do not cause severe symptoms in most cases. However, persistent infection can lead to cancer; therefore, low-risk infections must be monitored (Lacey *et al*., 2006; Watson *et al*., 2015).

While many countries have national vaccination programs targeting adolescents and young adults as part of public health policy and widely recognize the importance of prevention, only a few extend these programs to older adults (Dibble *et al*., 2019; Bruni *et al*., 2021).

The incidence of HPV varies by ethnicity (Bruni *et al*., 2023), whereas that of different types of carcinomas varies by sex. For example, oropharyngeal cancer is more common in men than in women in the USA (Van Dyne *et al*., 2018). Although age-specific HPV prevalence varies across populations, population-based prevalence data remain lacking in some countries (Chan *et al*., 2019; Bruni *et al*., 2021).

Previous studies have primarily examined the types of HPV infections in younger individuals or older patients with cancers, such as oropharyngeal squamous cell carcinoma (Dickstein *et al*., 2020; Dave *et al*., 2017). However, research on the prevalence and genotype distribution of HPV infections in older adults, particularly older men, remains limited (Han *et al*., 2017; Lannér and Lindström, 2020). While most studies have addressed HPV prevalence, few have focused on HPV types in older men. Thus, examining the prevalence and genotype distribution of HPV infections in the general older population is necessary.

Globally, the average life expectancy has increased compared to that in the past, highlighting the significance of social and economic aspects of health-related issues. HPV-induced diseases can affect the quality of life and social and economic burden of older adults. Therefore, this study analyzed the prevalence of HPV positivity and co-infection by age and HPV type in Korean older adults and identified differences in HPV positivity and HPV type by age in male and female older adults.

In addition, based on reports that biological, immunological, and cognitive characteristics differ among older adults and are not homogeneous by age (North and Fiske, 2013; Montgomery and Shaw, 2015; Hanyu *et al*., 2024), we aimed to identify differences in HPV infection rates by age. This study may contribute to expanding cervical cancer screening for older women and improve the level of evidence for preventing and managing HPV infections in the older adult population.

Materials and Methods

Study Population

In this research, we evaluated data from individuals aged ≥65 years, focusing on HPV test results obtained between January 2020 and June 2023 at the U2Bio outsourced testing center, which caters to hospitals across the country. Male participants primarily underwent testing to address concerns regarding potential Sexually Transmitted Infections (STIs), whereas female participants underwent routine health screenings or investigations related to suspected STIs at the hospitals.

Data Privacy Measures

All personal information except sex and age has been removed to protect privacy. The only data used in the study were sex, age, and HPV test results. Only test-result data were retained for analysis.

Data Collection

All tested data, inclusive of various sample types, were included in the analysis. Women underwent a higher number of tests than men due to state-supported cervical cancer screening.

Laboratory Procedures

Following sample collection, DNA was extracted using the QIAsymphony system (QIAGEN, Hilden, Germany). Multiplex real-time polymerase chain reaction was performed using the OmniPlex™-HPV kit (Genematrix, Seongnam, Korea) along with the CF × 96 real-time thermocycler (Bio-Rad, Hercules, CA, USA).

HPV Typing

In total, 41 HPV types were identified and categorized into 12 high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) and 29 low-risk (6, 11, 26, 30, 32, 40, 42, 43, 44, 53, 54, 55, 61, 62, 66, 67, 68, 69, 70, 71, 72, 73, 74, 81, 82, 83, 84, 87 and 99) types.

Quality Control

All inspection procedures strictly adhered to the manufacturer's instructions throughout the study, ensuring the reliability and consistency of the results.

Procedure

Swabs and other samples, including tissue, urine, semen, and prostatic fluid, were obtained. No data were collected on the anatomical site from which the swab was taken. The sample selection procedure was conducted as shown in Fig. (1). In total, 32,565 HPV samples tested between January 2020 and June 2023 were collected. Some collected samples had missing data (n = 776) or did not meet the inclusion criteria (n = 30,622); thus, 31,398 samples were excluded. The final study included HPV samples from 84 men and 1,083 women.

Statistical Analyses

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) and graphs were generated using R Studio version 2023.06.1 (R Studio, Inc., Boston, MA, USA).

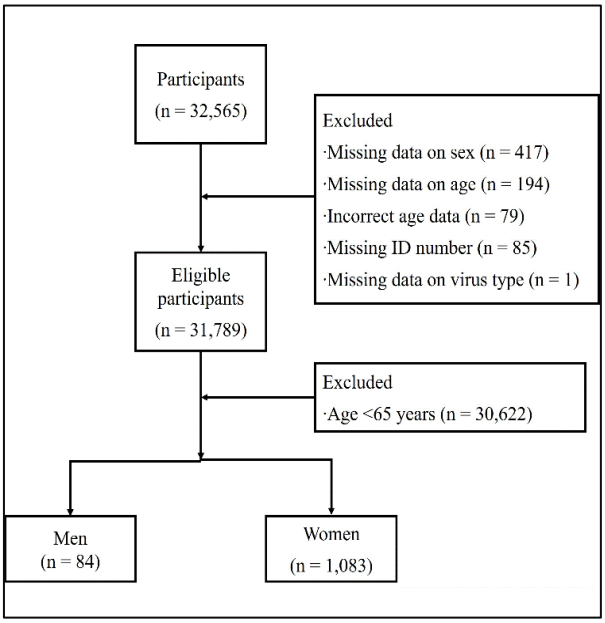

Fig. 1: Flow chart of the study sample selection

Frequency analysis was performed to calculate the positivity rates of HPV, stratified according to sex, age group, and HPV type. During this analysis, age groups were categorized as 65-74 and ≥75 years.

Independent t-tests were performed to determine the difference in mean age between the HPV-positive and HPV-negative groups. In addition, chi-square tests were performed to determine the difference in HPV frequency between the 65-74 and 75-99 years age groups for each sex and the difference in frequency by HPV type. A p-value of <0.05 was considered statistically significant. The HPV positivity rate in this study was defined as having one or more positive results among the 41 types of HPV, regardless of the specific HPV virus type.

Ethics Consideration

This study was approved by the Institutional Review Board (IRB) of U2Bio (IRB No. 2023066) and conducted in accordance with the principles of the Declaration of Helsinki. As the data were retrospectively analyzed and the personal information of the patients was not used, the requirement for informed consent was waived by the IRB of U2Bio.

Results

The positivity rates for men and women aged ≥65 years were 60.7% and 34.9%, respectively (Table 1). When stratified by age, the positivity rates for those aged 65-74 years were 61.1% for men and 39.9% for women, whereas for those aged 75-99 years, the rates were 58.3% for men and 36.9% for women. The positivity rates were lower in the 75-99 years group than in the 65-74 years group in both men and women; however, this difference was not statistically significant (men: $\chi^2 = 0.0333$, $p>0.05$; women: $\chi^2 = 0.5122$, $p>0.05$).

The highest positivity rates in men and women aged >65 years were observed for HPV types 6 (41.7%) and 52 (5.6%), respectively (Table 2). Additionally, HPV type 11 (16.7%) and types 16, 40, and 55 (7.1%) were the second and third most significantly positive in men ($\chi^2 = 525.8707$, $p<0.0001$), respectively. In contrast, HPV types 62 (5.4%) and 53 (5.3%) showed the second and third highest positivity rates in women ($\chi^2 = 526.7876$, $p<0.0001$), respectively. Positivity rates for HPV types were significantly different between the sexes ($\chi^2 = 239.7447$, $p<0.0001$). Among men, the highest rate of high-risk HPV positivity was observed for type 16, followed by types 35 and 39, while the highest rate of low-risk HPV positivity was observed for type 6, followed by type 11. Among older adult women, the highest high-risk HPV positivity rate was observed for type 52, followed by types 16 and 51, whereas the highest low-risk HPV positivity rate was observed for type 62, followed by type 53. High-risk HPV types identified in men aged ≥65 years included 16, 31, 33, 35, and 39, whereas those identified in women were types 18, 45, 51, 56, and 59. Low-risk types identified in men were 6, 11, 26, 30, 32, 40, 42, 44, 53, 54, 55, 61, 62, 67, 68, 71, 73, 74, 81, 82 and 84, whereas those in women were 43, 66, 69, 70, 72, 72, 83, 87 and 99, in addition to the types identified in men.

Table 1: Age-related HPV positivity rates

	Men (n = 84)			Women (n = 1,083)		
Age group	Negative (mean [±S.D.] or n)	Positive (mean [±S.D.] or n)	Positivity rate (%)	Negative (mean [±S.D.] or n)	Positive (mean [±S.D.] or n)	Positivity rate (%)
Mean age (years)	70.33 (±5.35)	69.47 (±4.86)	-	70.11 (±4.48)	69.75 (±4.28)	-
	t-value = 0.76, p = 0.4474			*t*-value = 1.32, p = 0.1875		
Total	33	51	60.7	656	427	34.9
65–74	28	44	61.1	555	368	39.9
75–99	5	7	58.3	101	59	36.9
	$\chi^2 = 0.0333$, p = 0.8553			$\chi^2 = 0.5122$, p = 0.4742		

HPV, human papillomavirus, S.D., standard deviation

Table 2: Positivity rates for different HPV types in older adults

Category	Type	Men (n = 84)			Women (n = 1,083)		
		n	%	χ^2 (p-value)	n	%	χ^2 (p-value)
High risk	16	6	7.1	525.8707 (<0.0001)	30	2.8	526.7876 <0.0001)
	18	0	0.0		10	0.9	
	31	1	1.2		7	0.6	
	33	1	1.2		5	0.5	
	35	2	2.4		8	0.7	
	39	2	2.4		21	1.9	
	45	0	0.0		3	0.3	
	51	0	0.0		30	2.8	
	52	1	1.2		61	5.6	
	56	0	0.0		10	0.9	
	58	1	1.2		24	2.2	
	59	0	0.0		11	1.0	
Low risk	6	35	41.7		33	3.0	
	11	14	16.7		8	0.7	
	26	1	1.2		1	0.1	
	30	1	1.2		11	1.0	
	32	2	2.4		8	0.7	
	40	6	7.1		9	0.8	
	42	3	3.6		27	2.5	
	43	0	0.0		11	1.0	
	44	2	2.4		21	1.9	
	53	1	1.2		57	5.3	
	54	3	3.6		17	1.6	
	55	6	7.1		12	1.1	
	61	1	1.2		40	3.7	
	62	2	2.4		59	5.4	
	66	0	0.0		14	1.3	
	67	2	2.4		11	1.0	
	68	2	2.4		29	2.7	
	69	0	0.0		3	0.3	
	70	0	0.0		34	3.1	
	71	2	2.4		30	2.8	
	72	0	0.0		17	1.6	
	73	2	2.4		3	0.3	
	74	2	2.4		45	4.2	
	81	2	2.4		31	2.9	
	82	1	1.2		7	0.6	
	83	0	0.0		5	0.5	
	84	3	3.6		18	1.7	
	87	0	0.0		24	2.2	
	99	0	0.0		0	0.0	

Table 3: HPV co-infection positivity rates for each sex

Sex/age group	Single	2 or more	χ^2 (p-value)[b]	2	3	4 or more	χ^2 (p-value)[b]
	n (%)[a]	n (%)[a]		n (%)[a]	n (%)[a]	n (%)[a]	
Male (n = 84)[a]							
Total (n = 51)	27(32.1%)	24(28.6%)	1.9037 (0.3860)	8(9.5%)	9(10.7%)	7(8.3%)	12.9708(0.0114)
65–74	25(29.7%)	19(22.6%)		8(9.5%)	8(9.5%)	3(3.6%)	
75–99	2(2.4%)	5 (6.0%)		0(0.0%)	1(1.2%)	4(4.8%)	
Female (n = 1,083)							
Total (n = 427)	229 (21.1%)	198 (18.3%)	1.5041 (0.4714)	104(9.6%)	43(4.0%)	51 (4.7%)	3.5997(0.4629)
65–74	201 (18.5%)	167 (15.4%)		89(8.2%)	38(3.5%)	40 (3.7%)	
75–99	28 (2.6%)	31 (2.9%)		15(1.4%)	5 (0.5%)	11 (1.0%)	

a. N, total number of participants; n, number of positive cases; % positivity rate
b. Difference in HPV positivity rates by age in older adult men/older adult women

The single-infection positivity rates for men and women were 32.1-21.1%, respectively, whereas the co-infection positivity rates for men and women were 28.6-18.3%, respectively (Table 3). In older adult men, when comparing those aged 65-74 and 75-99 years, the former had the highest positivity rates for single HPV infections (29.7%), followed by double and triple HPV infections (9.5%). In older adult women, when comparing those aged 65-74 and 75-99, the former had the highest number of single HPV infections (18.5%) and the highest number of double HPV infections (8.2%).

Discussion

The HPV positivity rates by age or sex were higher in men than in women aged ≥65 years and the prevalence of HPV between the two age groups in both sexes did not differ. In this study, the overall HPV-type positivity rate among women was 34.9%; however, among 1,784 Swedish women aged ≥60 years, the positivity rate was notably low at 5.4% (Lannér and Lindström, 2020). Similarly, this study reported a higher positivity rate than that observed in a study of 5,906 Thai women aged 20-70 years, which revealed an HPV positivity rate of 11.0% among those aged 61-70 years (Kantathavorn *et al*., 2015). In addition, a meta-analysis combining data from 16 studies across several countries, including the United States, China, and Spain, estimated the prevalence of all types of HPV in men at 49% (Rodríguez-Álvarez *et al*., 2018); however, this study reported a high prevalence of 60.7%. Older men exhibited higher rates of HPV positivity than older women, likely because men primarily visited the clinic for symptoms of suspected STIs, whereas women sought health screening and diagnosis of suspected STIs. This could also be attributed to the biological differences between men and women. For example, HPV can cause infections in various sites in men, including the oral cavity and anus, in addition to the genitals. The high risk of infection at multiple sites, particularly through oral-genital contact, may be related to the high prevalence of high-risk HPV types in men.

Previous studies have suggested that latent reactivation, increased new sexual partners and cohort effects may explain the high prevalence of HPV in the older female population in Australia (Chow and Fairley, 2015). These differences in HPV positivity rates between older men and women may be related to various factors, including ethnicity, region, sample type, and study design (Chow and Fairley, 2015). Furthermore, the high positivity rates among older adult men and women in our study may be owing to the high proportion of participants who primarily visited the clinic because of suspected STIs.

HPV is involved in the pathogenesis of cervical cancer in women and penile, anal, and oropharyngeal cancers in men (Spînu *et al*., 2021). Previous studies have reported that the burden of HPV-related diseases is high in both men and women (McDonald *et al*., 2017). Many countries exclude older populations from vaccination programs for cost-effectiveness (Spînu *et al*., 2021). Patients aged ≥65 years included in this study were born prior to the implementation of the national HPV vaccination programs and therefore did not receive HPV vaccine. Epidemiologically, older men infected with HPV can transmit HPV to older women through sexual activity (Spînu *et al*., 2021). The high positivity rate among older men suggests that older women are also likely to be infected with HPV, emphasizing the importance of HPV prevention and control in men as a strategy to protect women's health.

In this study, various high- and low-risk HPV types were identified in HPV-positive older adults. HPV type 6 (41.7%) exhibited the highest positivity rate among older adult men, followed by HPV type 11 (16.7%) and 16/40/55 (7.1%). HPV type 52 (5.6%) had the highest positivity rate among older adult women, followed by HPV types 62 (5.4%) and 53 (5.3%). A study investigating the rate of HPV infection in postmenopausal women reported that the most common HPV infection types were 52, 53, 58, and 16 (Rositch *et al*., 2012), which is consistent with the findings of this study. In this study, the positivity rate of high-risk HPV was the third highest (type 16) in older adult men and the highest (type 52) in older adult women.

These results differ from those of a previous study involving 814 female patients in South Korea, revealing that type 16 was the most common high-risk HPV type for single infections (Kim *et al*., 2022). Another meta-analysis found that the most prevalent HPV type in Asia was HPV 16, followed by HPV 52, in women with cervical abnormalities (Okoye *et al*., 2021). The results also differ from those of a study among men in the general population in China, where the most common high-risk HPV type was type 52 (Hu *et al*., 2022).

This difference is likely attributable to the difference in mean age (women: 55.5 years, men: 38 years), patient characteristics such as abnormal cytology or histology results, and ethnicity.

Previous studies have revealed that persistent high-risk HPV infection is associated with a higher risk of developing precancerous diseases, with HPV type 16 being the most common cervical carcinogen (Chan *et al*., 2019). Despite its rarity, type 53 is reportedly associated with cervical cancer in older adult women (Zappacosta *et al*., 2014). The identification of recent or long-standing infection with high-risk HPV type 16 cannot be determined. However, some older adult women who participated in this study showed a positivity rate of 2.8% for HPV type 16, indicating that they may be exposed to the risk of

developing precancerous diseases associated with persistent infection.

The current HPV vaccine, Gardasil 9, protects against HPV types 6, 11, 16, and 52 (Lee, 2021). In South Korea, men and women aged >65 years are not mandatory recipients of the HPV vaccination, and older adult men are not subjected to mandatory HPV screening. Some studies have suggested the expansion of cervical screening in women aged ≥65 years (Ernstson *et al*., 2019). However, no consensus has been reached regarding the age at which cervical cancer screening can be halted (Sherman *et al*., 2015). Age-based management strategies are required to prevent HPV transmission in older adult men and women.

In this study, the single-infection positivity rates for men and women aged 65 years were 32.1-21.1%, respectively. The positivity rates for co-infection were 28.6-18.3% in older adult men and women, respectively. Although not consistent with the co-infection positivity rates reported in this study, several previous studies have reported HPV co-infection in older adults (Ingles *et al*., 2015; Hermansson *et al*., 2018). Patients with cervical cancer had higher rates of co-infection with HPV. However, whether co-infection poses a higher clinical risk than a single infection remains controversial (Luo *et al*., 2023). The possible occurrence of competition or cooperation between the different HPV genotypes is still unclear (Luo *et al*., 2023). The combination of high-risk HPV may vary according to the demographic characteristics (Luo *et al*., 2023); the prevalence of multiple infections is influenced by multiple factors, including age and immune status, socioeconomic condition, and vaccination statuses (Soto-De Leon *et al*., 2011; Kim *et al*., 2022). Sexually active individuals, including women having multiple sexual partners and more frequent sexual intercourse, have the highest risk of developing multiple infections (Dickson *et al*., 2013; Kops *et al*., 2021). An immunocompromised state has also been suggested to cause an increase in the incidence of multiple infections in postmenopausal women (Rositch *et al*., 2012). Further research is needed to study the effects of specific HPV combinations on co-infection, as well as the differences between genotypes (Luo *et al*., 2023).

Life expectancy has increased globally to 73.4 years in 2019, compared with that in the past (66.8 years in 2000) (Global Health Estimates: Life Expectancy and Leading Causes of Death and Disability). As the global older adult population increases, better knowledge of the prevalence of HPV infection and infection-prevention management for healthy sexual behavior in older adult men and women is needed to improve health-related quality of life in older adults (Lester *et al*., 2020).

A strength of this study is that it reports HPV positivity rates in the Korean older adult population, particularly among men. This may be a strength, as the literature on the prevalence and incidence of HPV infection in older adults is scarce, especially with limited data on older adult men. The information in this study can also improve the current understanding of infection characteristics in older adults in Korea.

This study has a limitation in that the cross-sectional results of HPV positivity do not confirm if the infections are newly acquired or represent reinfections. Future research should focus on determining whether HPV positivity indicates reinfection or reactivation by analyzing the characteristics and genetic mutations of the virus, as well as evaluating clinical symptoms. Additionally, conducting a long-term comprehensive study is warranted.

Conclusion

Regular HPV infection screening is necessary not only for younger and middle-aged individuals but also for older adults. Therefore, age-based healthcare should be provided to prevent HPV transmission. The findings of this study could help in improving the understanding of HPV in older adult populations, informing healthcare strategies for older adults, and contributing to global knowledge on HPV epidemiology. This study offers valuable data and insights, reinforcing and potentially broadening the current body of knowledge in this field.

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Author's Contributions

Jieun Hwang and Hee Seung Song: Conceptualization methodology, writing-original draft preparation writing-review, and editing, contributed equally to this work.

Jang Mook Kim: Formal analysis, investigation, and data curation.

Jae Kyung Kim: Formal analysis, investigation, data curation, writing-original draft preparation, writing-review and editing.

All authors have read and agreed to the published version of the manuscript.

Ethics

This study was approved by the IRB of U2Bio (IRB no. 2023066) and conducted in accordance with the principles of the Declaration of Helsinki. As the data were retrospectively analyzed and the personal information of the patients was not used, the requirement for informed consent was waived by the IRB of U2Bio.

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