



Prevalence and economic burden of male anogenital wart in Korea: A population-based big data analysis from 2007 to 2018

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Purpose: To investigate the prevalence of anogenital warts (AGW) caused by human papillomavirus in men and the characteristics and changes of the disease in Korea.

Materials and Methods: From 2007 to 2018, male AGW corresponding to the International Classification of Disease-10 A63.0 were targeted. Through a big data analysis of the Health Insurance Review & Assessment Service, data of patients diagnosed with AGW as either the main or secondary diagnosis were extracted. The overall prevalence and prevalence by age were calculated through the population by year and the population by 5-year-old unit of the National Statistical Office. Additionally, the amount accrued through the disease code was confirmed and compared as AGW-related medical expenses.

Results: The annual number of patients increased by 3.5 times from 32,709 in 2007 to 114,734 in 2018. Additionally, the annual prevalence increased by 3.34 times from 132.83 per 100,000 to 443.57. The age-specific prevalence was the highest among the 25- to 29-year age group. The highest prevalence was observed in the 25- to 29-year age group in 2018 (1,492.15 per 100,000), and the lowest was noted in the 10- to 14-year age group in 2014 (7.28 per 100,000). AGW-related medical expenses increased by approximately 9.76 times from US\$ 2,789,215.1 in 2007 to US\$ 27,227,254.9 in 2018.

Conclusions: In Korea, cases of male AGW are increasing yearly, with the 25- to 29-year age group having the highest prevalence. Medical costs related to AGW are also increasing tenfold. For male AGW, further studies and national interventions are needed.

Keywords: Condylomata acuminata; Human papillomavirus; Male; Prevalence

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INTRODUCTION

AGW are sexually transmitted infections caused by human papillomavirus (HPV) and are the most common HPV-related disease [1]. HPV is a small double-stranded DNA virus, with >220 types; of these, 40 types cause various diseases

around the genital area [2]. It causes penile cancer in men, and cervical and vulvar cancers in women, and is closely related to head and neck cancers, AGW, and anal cancer in both men and women [3]. Malignant tumors are caused by high-risk HPV subtypes and low-risk subtypes associated with benign diseases, such as AGW [4,5]. Malignant tumors

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are caused by HPV, and vaccination against the virus prevents the development of cancer; this has attracted much attention worldwide. Many countries worldwide are making great efforts to combat these cancers in women. Contrarily, HPV infection in men has received relatively little attention, as compared to that in women. The names of the virus and vaccine were initially called “cervical cancer virus” and “cervical cancer vaccine,” respectively. The disease was recognized as being unrelated disease to men, as they have no uterus; therefore, it has been identified as a disease limited to women. For these reasons, there is a lack of interest in HPV-related diseases in men, resulting in a scarcity of related studies. Even in Korea, which has the highest number of HPV-related diseases in men, studies on AGW are few [6-8]. However, recently, the number of HPV-related head and neck cancers is higher in men than in women [9], resulting in changes in the U.S. Food and Drug Administration guidelines, including added indications for vaccines.

Cervical or head and neck cancers are the most commonly recognized HPV-related diseases. However, the disease with the highest number of cases induced by HPV is AGW. It occurs mainly in sexually active age groups and is also known as one of the most common sexually transmitted diseases [3]. In foreign countries, relatively many studies on AGW including the prevalence have been conducted. Contrarily, in Korea, epidemiologic studies on AGW or their disease characteristics are scarce. If various disease characteristics, such as prevalence, type of treatment, regional and age-specific characteristics, and cost can be found, then the disease characteristics of domestic AGW can be identified and used for treatment or prevention, or the rationale for male vaccination we can provide data on feasibility. Several cost-effectiveness studies conducted domestically to include boys in the national immunization program (NIP) have shown that the cost-effectiveness of vaccinating females is higher than that of males. However, during the evaluation of epidemiologic studies, there were opinions that the burden of HPV-related diseases in males has been underestimated due to a lack of prevalence studies on HPV-related diseases among men in Korea. Although a nationwide big data analysis study was conducted in 2018 [10], these findings were not fully incorporated into the analysis. In order to establish evidence for male vaccination, as done in other countries, there is a need for more detailed prevalence studies on AGW, which accounts for the largest proportion of HPV cases in men. Therefore, in addition to the study conducted in 2018 by Park et al. [10], there was a recognized need for a more detailed analysis focusing on specific age groups and male patients.

The present study aimed to investigate the prevalence of AGW caused by HPV in men and the characteristics and changes of the disease by analyzing big data on health care in Korea.

MATERIALS AND METHODS

1. Patients

Among the patient data registered in the National Health Insurance Review & Assessment Service (HIRA), men diagnosed with the International Classification of Disease (ICD)-10 code A63.0 anogenital (veneral) wart (AGW) from 2007 to 2018 were targeted. The prevalence and age-specific characteristics, related medical costs, treatment trends and analysis, and regional characteristics were analyzed. The data were extracted from the HIRA big data system, with project number M20200205277.

2. Prevalence (crude and age-specific)

1) Annual crude prevalence

The annual prevalence was analyzed as the number of patients extracted compared to the number of the population in that year. It was calculated based on the number of men among Korean citizens up to December of the year confirmed in the Republic of Korea Census by the National Statistical Office. It was calculated as the number of patients per 100,000 population, analyzed from 2007 to 2018. Additionally, the actual growth rate reflecting the population growth rate during the period was also confirmed.

2) Age-specific prevalence

Due to the nature of the disease, the prevalence by age is also an important indicator. Therefore, the population was divided into 5-year-old units, and the number of patients for each age group was extracted within the study period. Additionally, the prevalence by age was extracted from the number of patients in the relevant population group in the current year as the 5-year-old unit population confirmed through the Republic of Korea census. Moreover, the maximum and minimum values of the prevalence were confirmed.

3. AGW-related medical cost

During the entire period, the medical expenses of patients diagnosed with A63.0 due to the corresponding main disease or injury from the main disease were defined as disease-related expenses. Among the patients with the corresponding diagnosis, patients with 0 won in terms of the amount of treatment were excluded from the analysis. The

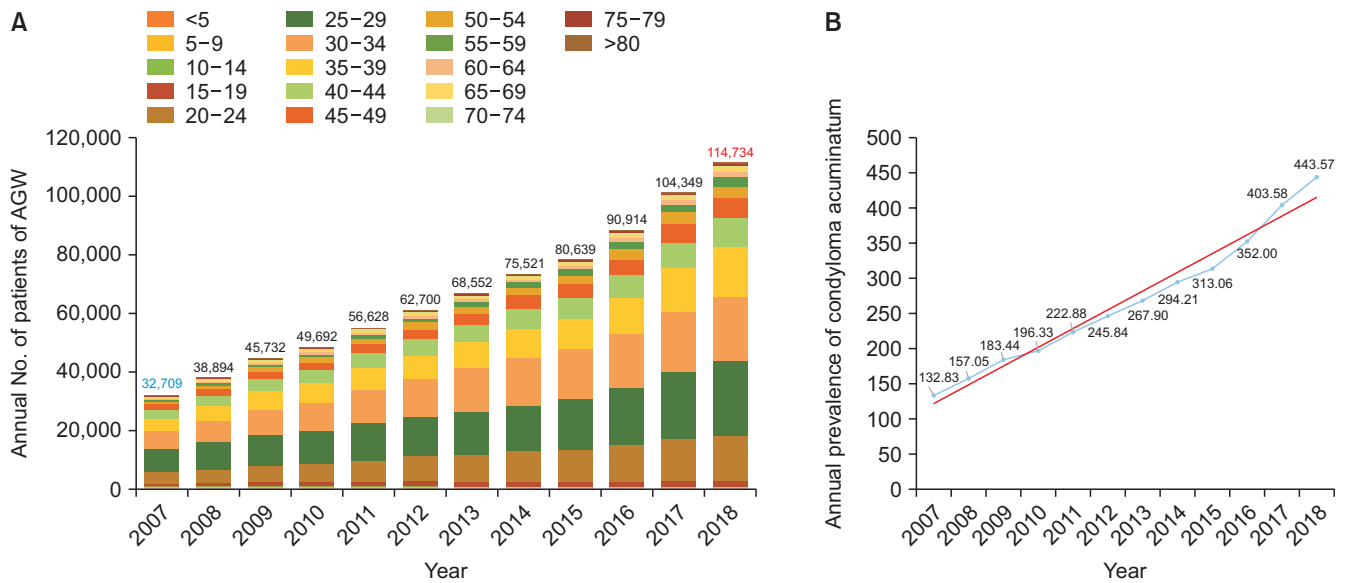


Fig. 1. Annual number of patients with and prevalence (per 100,000 person) of anogenital warts (AGW) from 2007 to 2018 (including the 5-year age group). (A) Annual number. The annual number of patients with AGW increased yearly, showing a 351% increase in the number of patients over 10 years. (B) Crude prevalence. In male AGW cases, the prevalence per 100,000 also showed an increase in the number of patients of more than three times.

cost was analyzed by including the entire amount entered in the specific disease, including diagnosis and treatment, as related costs, regardless of the treatment method. The won-dollar exchange rate was converted to the won-dollar exchange rate of 2018, which was the last year of the analysis period, and the exchange rate for that year was 1,100.58 won per dollar (based on data from the National Statistical Office, https://kosis.kr/statHtml/statHtml.do?orgId=101&tblId=DT_2KAA811).

4. Statistical analysis

The data were extracted from the HIRA big data system, with project number M20200205277. Analysis was performed at Wonju data center, and the SAS 9.4 program (SAS Institute) was used for statistical analysis. The data was analyzed using descriptive statistics.

5. Ethics statement

The study protocol was approved by the Institutional Review Board of The Catholic University of Korea (approval number: XC19ZIDI0101).

The requirement for obtaining consent from the research participants was waived as publicly available data were used and no personal information was included in the manuscript and accompanying documents.

RESULTS

1. Annual number of patients and prevalence

In 2007, the number of male patients diagnosed with AGW was 32,709, which increased steadily yearly; in 2018, it was 114,734, confirming an increase of 351% (Fig. 1A). The number of patients increased by approximately 6,835 per year. During the period, the male population increased by 5% from 24,624,127 to 25,866,129, indicating an actual increase rate of 334%, which confirms a more than threefold increase in patients. During the period, the annual prevalence increased by 334%, from 132.83 cases in 2007 to 443.57 cases in 2018 per 100,000 people (Fig. 1B). Overall, there was a steady increase in the number and prevalence of patients.

2. Age-specific prevalence

In the 5-year unit analysis, the 25- to 29-year age group had the highest number of patients in all years (Fig. 2). Additionally, starting from the 15- to 19-year age group, visible changes were observed until 50-54 years of age; after 55-59 years, a relatively plateau pattern was observed. Patients aged 15-59 years (red area) account for approximately 70% of the total population, but >93% of the patients and this age group accounts for most of the total number of patients. It can be seen that age is an important factor influencing the occurrence of the disease (Table 1).

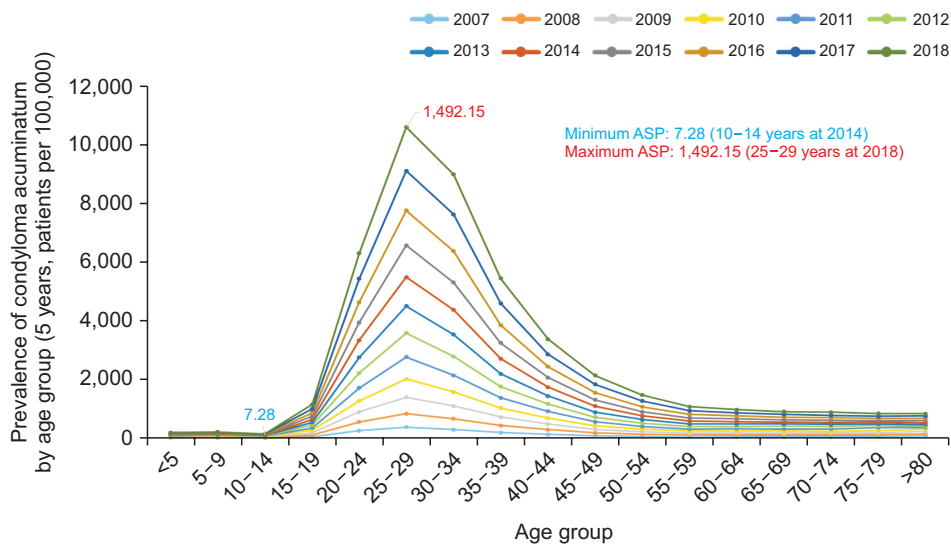


Fig. 2. Prevalence of anogenital warts by age group (5 years, patients per 100,000). ASP, age-specific prevalence.

3. AGW-related medical cost

AGW-related medical costs increased from US\$ 2,789,215.1 in 2007 to US\$ 27,227,254.9 in 2018, showing an increase of 9.76 times (Fig. 3). Regarding the change in cost by age, a decrease of approximately 24% was confirmed in the 0- to 9-year age group, and an increase was observed in all other ages. In the 10-year age group, the increase in medical expenses in their 20s increased the most at 1,238.1%, followed by those in their 50s (1,019.5%) and those in their 30s (899.4%). Finally, the increase in cost was clearly noted even in the elderly population in their 70s (Table 2).

DISCUSSION

AGW is among the most common sexually transmitted infections and has the largest number of patients among the HPV-related diseases [1]. However, because it is not caused by high-risk groups such as 16 and 18, which cause malignant tumors, but by low-risk groups, 6 and 11, which are forms that cause benign skin diseases, it was considered a mild, non-life-threatening condition, thereby receiving relatively little attention [11]. In most cases, AGW was treated in clinics by excision, cryotherapy, and electrocauterization under local anesthesia, or by treatment with drugs, such as podophyllin or imiquimod [12]. In fact, most HPV-related diseases are related to cervical cancer; thus, research and policies focusing on women and those on vaccination have been mainly conducted.

Similar to our study findings, the prevalence of AGW is showing a gradual increase. Moreover, age is considered an important factor to consider and is thought to cause more serious problems in cases of HIV infection. In a systematic review, the global incidence of AGW was approximately

194.5 per 100,000, with the incidence being higher in men than in women. As of 2007, the prevalence was slightly lower than that of Spain or Canada, and much lower than that of Mexico or the United States [1]. In addition, there were no studies other than domestic data on continuous prevalence, and furthermore, population-based analysis studies were difficult to confirm. However, based on domestic data, AGW among men in Korea increases very steeply in about 10 years. It can be seen as having greater significance. The peak incidence for women and men is 20-24 years and 25-29 years, respectively, which was consistent with the peak age of men identified in our study. In Korea, the rate of increase was very steep, from approximately 132 to 443 per 100,000 people. Additionally, these diseases peak during the sexually active years, and, in 2018, there were 1,492.15 cases per 100,000 people (1.5 cases per 100 people). Therefore, it is thought that more intensive management, use of condoms, and publicity and notification of diseases should be implemented for this age group.

Additionally, the related cost increased by 9.76 times, which is a very rapid increase in a period of approximately 10 years, thereby increasing the burden. It was reported that the cost of illness in Peru in 2016 was USD 20,000,000 for men and USD 5,000,000 for women. In comparison, in Korea, the cost for men was USD 17,455,358, which was lower than that of Peru in the same year [13].

The number of HPV-related infections, including AGW, in men is increasing, and there are only few approaches to prevent them. In women, many efforts to prevent HPV-related diseases exist, such as early treatment through screening tests, national compulsory vaccination for adolescents, and follow-up vaccination. Further, in cervical cancer cases in Korea, the number of annual cases has been decreasing

Table 1. Age-specific (sexually active age group) characteristics

Age group	2007		2008		2009		2010		2011		2012		2013		2014		2015		2016		2017		2018	
	Patients	Population	Patients	Population	Patients	Population	Patients	Population	Patients	Population	Patients	Population	Patients	Population	Patients	Population	Patients	Population	Patients	Population	Patients	Population	Patients	Population
Age group	32,709	24,624,127	38,984	24,822,897	45,732	24,929,939	49,692	25,310,385	56,628	25,406,934	62,700	25,504,060	68,552	25,588,336	75,521	25,669,296	80,639	25,758,186	90,914	25,827,594	104,349	25,855,919	114,734	25,866,129
<5	161	1,201,209	198	1,183,217	207	1,167,689	241	1,185,537	243	1,198,629	276	1,194,460	221	1,183,212	173	1,178,326	145	1,162,807	143	1,129,953	160	1,066,180	150	1,012,380
5-9	311	1,589,915	255	1,464,571	252	1,385,903	296	1,278,040	265	1,218,866	225	1,214,863	200	1,199,677	208	1,184,754	231	1,203,174	166	1,215,209	192	1,211,669	180	1,196,477
10-14	193	1,867,106	286	1,803,423	311	1,744,514	219	1,706,007	224	1,635,253	227	1,544,170	175	1,465,338	101	1,387,285	162	1,278,769	135	1,219,887	163	1,216,208	167	1,200,639
15-19	804	1,722,229	1,153	1,804,831	1,411	1,854,634	1,641	1,892,719	1,567	1,882,958	1,788	1,846,162	1,617	1,801,265	1,764	1,743,200	1,831	1,702,043	1,905	1,632,122	2,112	1,541,483	2,210	1,461,559
20-24	4,554	1,756,562	4,952	1,648,863	5,592	1,637,339	6,159	1,616,287	7,369	1,688,523	8,934	1,752,677	9,661	1,802,320	10,840	1,852,508	11,352	1,886,202	13,018	1,877,127	14,742	1,840,481	15,538	1,795,166
25-29	7,836	2,056,125	9,491	2,079,081	11,285	1,999,170	11,936	1,913,337	13,482	1,811,906	13,947	2,078,803	15,218	1,649,886	16,147	1,638,106	17,749	1,641,611	19,966	1,682,988	23,651	1,747,478	26,809	1,796,667
30-34	6,295	2,102,838	7,407	1,994,183	8,555	1,997,288	9,582	2,017,088	11,698	2,053,846	13,247	2,078,373	15,593	2,085,473	16,968	2,004,817	17,777	1,911,972	19,308	1,806,754	21,328	1,702,336	22,395	1,645,627
35-39	4,630	2,328,233	5,493	2,326,763	6,626	2,297,210	6,966	2,255,652	7,537	2,157,764	8,029	2,085,311	8,687	2,005,223	10,182	1,980,982	10,695	2,007,424	12,493	2,045,265	15,372	2,070,532	17,593	2,077,946
40-44	2,885	2,139,080	3,552	2,183,128	4,266	2,221,799	4,590	2,294,124	5,374	2,341,732	6,033	2,366,703	6,246	2,344,220	7,087	2,311,387	7,209	2,238,667	7,944	2,143,639	8,777	2,072,984	10,296	1,993,955
45-49	1,862	2,194,686	2,196	2,227,093	2,591	2,217,365	2,714	2,219,528	3,107	2,176,857	3,355	2,143,613	3,706	2,196,548	4,630	2,232,995	4,863	2,266,945	5,654	2,317,182	6,581	2,343,868	7,006	2,322,659
50-54	1,105	1,658,052	1,309	1,829,706	1,647	1,939,614	1,853	2,075,192	2,080	2,175,707	2,437	2,226,268	2,752	2,228,829	2,794	2,217,165	3,013	2,177,823	3,602	2,139,711	4,202	2,109,201	4,349	2,162,701
55-59	525	1,193,630	828	1,249,093	858	1,322,034	1,032	1,468,249	1,117	1,598,548	1,400	1,689,298	1,669	1,812,276	1,832	1,920,820	2,200	2,018,507	2,510	2,120,391	2,765	2,172,196	3,073	2,176,502
60-64	469	938,689	598	989,786	749	1,041,371	837	1,113,044	824	1,133,757	865	1,189,791	1,035	1,216,918	1,013	1,290,056	1,337	1,411,839	1,559	1,540,582	1,741	1,630,378	1,936	1,751,203
65-69	399	830,648	544	879,481	570	878,816	659	886,479	625	886,144	825	893,794	711	943,198	716	994,183	749	1,050,474	981	1,072,395	1,010	1,128,219	1,106	1,155,935
70-74	338	547,611	349	606,143	379	646,459	410	675,908	543	713,163	646	779,224	594	796,139	511	800,094	658	801,927	731	806,680	633	820,056	879	869,294
75-79	162	284,446	208	319,313	222	350,568	324	394,812	425	433,883	327	467,062	279	503,314	320	540,915	324	564,174	429	600,607	499	662,122	607	680,342
>80	180	213,070	165	234,222	211	253,166	233	282,382	148	299,398	139	325,488	188	354,500	235	391,704	344	433,828	370	477,102	421	520,528	440	567,077
Ratio	93%	70%	93%	70%	94%	70%	94%	70%	94%	70%	94%	70%	95%	70%	96%	70%	95%	69%	95%	69%	95%	68%	95%	67%

recently [14]. Moreover, for AGW, as of 2012, the number of cases decreased in women [10]. However, in men, a persistent increase in the number of AGW has been confirmed in some studies, including the present study. HPV-related diseases also showed a steady increase. Due to the characteristics of the disease, screening tests are difficult for men, and confirmation is possible only when the disease occurs; thus, it is practically difficult to confirm whether an asymptomatic person is infectious by contact with urine or skin [15]. In general, visual inspection of the AGW is the only management and no other interventions are recommended. Therefore, screening tests are not recommended [16]. Additionally, the possibility of infection should be mentioned to the current partners of AGW patients. However, there is no need to inform future partners because the remaining period is unknown. It is generally difficult to distinguish recurrence from reinfection, and infection by other genotypes may occur even after the visible wart is treated. Therefore, it may be necessary to monitor the patients to determine if gross lesions will develop even after treatment.

Among the HPV-related diseases, including those presented in this study, several methods are effective in preventing various HPV-related diseases, especially in men, in addition to AGW [17]. However, in the current situation, methods to slow or prevent the increase the prevalence of the disease in Korea are few. Typically, vaccination and circumcision are preventive methods, but there are many difficult parts in the current domestic situation.

HPV vaccines known to be protective against HPV are not included in the NIP for men in Korea. More than 140 countries worldwide have immunization programs for women; 62 of which include immunization for men. Among the countries included in the Organization for Economic Cooperation and Development, only six countries including Korea, which ranks 18th among the top 18 countries by GDP (gross domestic product), provide vaccination to women. This policy reflects that women are vaccinated and the age of adaptation through catch-up vaccination is more economically effective because cost-effectiveness is generally observed. Moreover, to acquire herd immunity, approximately >75% of the total population for female vaccination and >50% for sex-neutral vaccination should be achieved [18]. However, for HPV-related diseases, achieving herd immunity takes a long time, and the current domestic vaccination rate is very far to achieve this. Therefore, vaccination for men also reduces the time required to achieve herd immunity, and men also need vaccination to cope with not only benign diseases as in this study, but also various male diseases, especially head and neck cancers, which are on the rise.

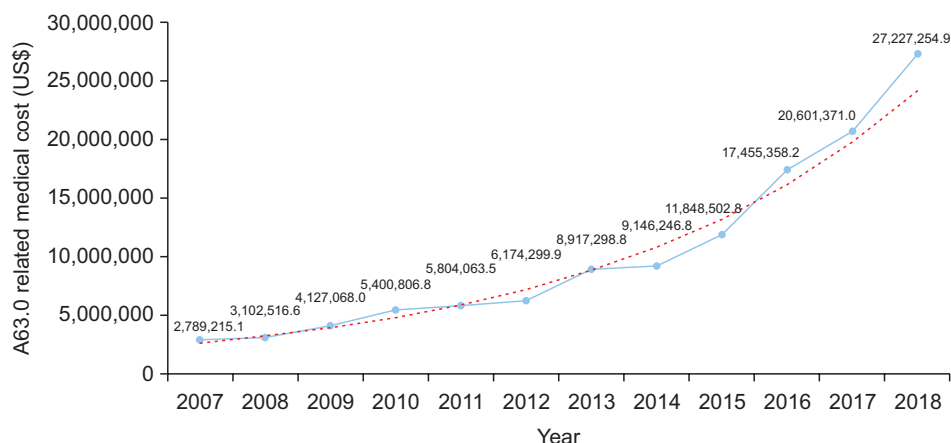


Fig. 3. Anogenital warts-related medical cost.

Table 2. Year-over-year costs and changes by age group in 10-year-old units

Age group	2007	2018	Increase rate (%)
0–9	29,533.6	22,381.5	-24.2
10–19	71,469.9	488,608.9	583.7
20–29	718,785.7	9,618,071.9	1,238.1
30–39	948,870.6	9,483,377.1	899.4
40–49	687,930.4	4,981,139.9	624.1
50–59	144,761.2	1,620,537.9	1,019.5
60–69	134,683.6	634,777.3	371.3
70–79	37,706.7	293,499.1	678.4
>80	15,473.3	84,861.2	448.4

For all costs, the 2018 won-dollar exchange rate of 1,100.58 won per dollar was applied.

In addition, circumcision reportedly has a preventive effect in various sexually transmitted diseases, including HPV, and it also shortens the period of natural elimination of the virus [19-21]. However, the circumcision rate has rapidly decreased in Korea and the procedure is currently hardly implemented. Moreover, for AGW, uncircumcised men with AGW on the penile skin have increased risk of developing urethral condyloma [22].

AGW needs to be investigated differently. When the HPV genotype analysis is performed through polymerase chain reaction test for lesions in AGW patients, low-risk types 6 and 11 are confirmed in most cases, but high-risk genotypes are also identified in a relatively larger proportion [8,23]. Although the disease itself is benign, women can be symptomatic and asymptomatic carriers due to coinfection of a high-risk genotype, which is why AGW in men should not be considered as a mere benign disease. Moreover, there is a risk of transmitting a high-risk genotype to women from these men through heterosexual intercourse. This is one of the reasons why HPV vaccination should be included in the

NIP even in men.

Our study also has several limitations. First, we could not confirm the recurrence or reinfection rate during the observation period. Second, it was difficult to ascertain the risk rate and location of the lesion according to the characteristics of the patient's AGW. AGW occurring in the foreskin, urethra, or urethral meatus should be analyzed differently. Third, it was difficult to confirm the characteristics of the disease itself because the individual disease pattern of each patient was not investigated. This may be a common disadvantage of research using big data obtained from a health insurance database. In the future, studies on individual characteristics, such as the circumcision type, number of lesions, presence of recurrence or not, and others are warranted to identify the characteristics of the disease. Fourth, the study showed a significant increase in costs compared to the rise in prevalence. However, since the current research only analyzed the total costs, it did not conduct a detailed analysis to determine whether the increase in costs was due to advancements in diagnostic methods and the resulting increase in testing, or an increase in the cost of treatment itself. Therefore, this study could not identify which factor had a greater impact on the cost increase. Further research on the contributing factors to the cost increase would be necessary, including a detailed cost analysis. Fifth, one of the limitations of big data research is that, in the case of HIRA big data, the analysis relies on diagnoses entered by health-care providers, which may not perfectly represent the actual number of patients. Although there may be some errors, the data still reflects population-based trends and continuous data, indicating the increasing trend of AGW in male patients.

According to our study data, the prevalence of AGW is rapidly increasing in Korea. However, measures to treat this disease are few. Thus, more research on the disease is needed

along with national interest. Although circumcision does not easily address this problem due to cultural and social factors, it can have a positive effect on disease prevention along with other preventive efforts such as vaccination and inclusion of men in the NIP.

Considering the nature of the disease, especially as a sexually transmitted infection, the disease itself is significant, but the social burden it imposes and its impact on public health policies are equally important. Therefore, beyond treating the disease itself, there is a need for policy approaches that include awareness, education, and prevention. It is true that policies have primarily focused on women because HPV is known to cause cervical cancer in women. However, during the period when attention to HPV-related diseases in men was lacking, we observed a notable increase in HPV-related head and neck cancers and a sharp rise in AGW among men. While HPV is associated with diseases in women, it is also a significant health, policy, and public health issue for men. Recognizing this, it is essential for the community to work together to address it. This effort should include education, awareness, prevention, policy incorporation, and changes in perception. The need for male vaccination has become increasingly evident.

CONCLUSIONS

The prevalence of AGW in men is rapidly increasing yearly and it increased by more than 3 times, with the highest prevalence observed among those aged 25–29 years in Korea. Medical costs related to the diseases are also increasing tenfold. It is necessary to develop measures targeting men aged 25–29 years, where the incidence is highest, and to adopt policy, educational, and preventive approaches, including the introduction of the NIP for boys, to address the increase in AGW among males.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Sangrak Bae and Seung-Ju Lee. Data acquisition: Sangrak Bae and Hong Chung. Statistical analysis: Sooyoun Kim, Sangrak Bae, and Jin Bong Choi. Data analysis and interpretation: Hong Chung, Seung-Ju Lee, and Sangrak Bae. Drafting of the manuscript: Hong Chung and Sangrak Bae. Critical revision of the manuscript: Sangrak Bae and Seung-Ju Lee. Obtaining funding: Sangrak Bae and Seung-Ju Lee. Administrative, technical, or material support: Sooyoun Kim and Jin Bong Choi. Supervision: Seung-Ju Lee and Sangrak Bae. Approval of the final manuscript: all authors.

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