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Estimating the Burden of Illness Related to Genital Warts in South Korea

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Title: Estimating the Burden of Illness Related to Genital Warts in South Korea

Running Head: Estimating the Burden of Illness Related to Genital Warts in South Korea

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ABSTRACT

Objectives: Estimate the prevalence of genital warts (GW) and GW-related healthcare resource use and costs among male and female patients in South Korea.

Design: To estimate GW prevalence, physicians in 5 major South Korean cities recorded daily logs of patients (N=71,655) between July 26 and September 27, 2011. Overall prevalence estimates (and 95% CIs) were weighted by the estimated number of physicians in each specialty and the estimated proportion of total patients visiting each specialist type. Healthcare resource use was compared among different specialties. Corresponding p-values were calculated using Mann-Whitney U tests.

Setting: The database covers 5,098 clinics for five major cities in South Korea: Seoul, Busan, Daegu, Kwangju, and Daejeon.

Participants: Primary care physicians (PCPs; general practice/family medicine), OB/GYNs, UROs, and dermatologists (DERMs) with 2-30 years' experience).

Results: The estimated overall GW prevalence was 0.72% (95% confidence interval [CI]: 0.67-0.76%). In women, GW prevalence was 0.63% (95% CI: 0.59-0.67%); in men it was 0.99% (95% CI: 0.95-1.03%), with peak prevalence among patients aged 18 and 24 years. Median costs for GW diagnosis and treatment for male patients were US $58.23 (South Korean Won [KRW] ₩ 66,857) and US $66.29 (KRW ₩ 76,113) for female patients.

Conclusions: The estimated overall GW prevalence in South Korea was 0.72% and was higher for male patients. The overall median costs associated with a GW episode were higher for female patients than for male patients.

Abstract word count: 232

Keywords: genital warts, healthcare resource use, South Korea

Article Summary:

- Physicians in 5 major South Korean cities recorded daily logs of patients (N=71,655).
- The prevalence of GW was estimated from physicians' daily logs of patients seen over a two-week period.
- Referral patterns, resource use, and costs for GW patients were captured through a 30-minute face-to-face physician survey from July 26, 2011 to September 27, 2012.
- Prevalence estimates were stratified by region, age group, gender, and physician specialty.

Strengths and Limitations:

Strengths of this survey include the limited existing research on GW prevalence and cost in South Korea and the presence of data across multiple physician specialties and geographic regions.

Limitations for this study include participating physicians having an increased likelihood to treat GW patients, possibly resulting in an overestimation of GW in South Korea. GW prevalence was not estimated from a random sample of physicians. National prevalence estimates were based on the physician population available from the IMS database, which may not include all physicians in South Korea. GW patients who did not seek healthcare treatment were not included. Potential bias may exist, related to the information source (physician survey) and the direction of bias is unknown.

BACKGROUND

Human papillomavirus (HPV) infections are the etiologic agents of genital warts (GW) and squamous intraepithelial lesions.[1] HPV is one of the most frequent sexually-transmitted viral infections[2-3] and has more than 130 identified virus types.[4] HPV 6 and 11 alone are estimated to cause approximately 90% of GW infections.[5] GW are highly infectious and nearly 65% of individuals with an infected partner develop lesions within 3 weeks-8 months from the first contact.[3,5] HPV prevalence varies by age and is higher among women and more common for young women with a new sexual partner.[6] Research suggests that an estimated 6.2 million new infections occur annually in individuals aged 14-44 years in the United States.

Data on national GW incidence by country are limited, and prevalence estimates by country range widely from 1.4% (Spain)[7] to 25.6% (Nigeria).[8, 9] In a recent systematic review undertaken to determine worldwide GW incidence and prevalence (from published data, January 2001-January 2012), GW incidence differed in regional distributions from 101-205, 118-170, and 204 new GW cases per 100,000 people in North America, Europe, and Asia, respectively. Age-specific GW incidence peaked for male patients aged 25-29 years and female patients 20-24 years, and remained significant in patients aged 30-45 years.[3]

Available GW treatments include patient-applied (home-based) chemicals (podofilox, imiquimod), provider-administered (office-based) chemicals (podophyllin, trichloracetic acid, interferon), and ablative treatment (cryotherapy, surgery, laser).[10] GW treatment and management can result in significant direct and indirect costs, and can cause a considerable financial burden, involving frequent physician office visits, medication application, and mechanical removal of warts. A study assessing incidence and economic burden on US commercially-insured patients reported estimated costs at $760 per 1,000 individuals in the

general population in 2004, with total costs exceeding $220 million.[11] Another study evaluating the economic burden of GW in Belgium, found similar conclusions related to overall costs. The estimated 7,989 annual number of diagnosed GW patients led to an estimated annual cost of €2.53 million.[12]

To date, there has been little research in South Korea to assess GW incidence and prevalence. A study conducted in South Korea among patients visiting urology (URO) and obstetrics/gynecology (OB/GYN) clinics observed a GW prevalence of 0.37% with a higher prevalence among young patients. Among patients with GW, 21% reported to have suffered a GW recurrence.[13] As such, the burden of GW may have a larger economic impact on society than previously estimated. Given the lack of available data in South Korea, the current study was designed to estimate GW prevalence in physician practices, and GW-related healthcare resource use and costs in South Korea among male and female patients aged 20-60 years.

METHODS

Study Design

This was a cross-sectional study conducted by survey in the major cities of South Korea.

Inclusion and Exclusion Criteria

Participating Physicians

Participating physicians were identified through the Korean Intercontinental Marketing Services (KR IMS) database, which contains nationwide clinics published by the Health Insurance Review and Assessment (HIRA) Service. The database covers 5,098 clinics for five targeted specialties in five major cities in South Korea: Seoul, Busan, Daegu, Kwangju, and Daejeon.

Physicians included in this study:

a) provided informed consent to participate and were specialists, including primary care physicians (PCPs; general practice/family medicine), OB/GYNs, UROs, and dermatologists (DERMs) with 2-30 years' experience);

b) devoted at least 30% of their time seeing and treating patients in outpatient visits, 3 or more work days per week (as opposed to inpatient surgeries, teaching, or other activities);

c) treated ≥75 patients in outpatient visits in a typical week; and

d) treated ≥50% of patients aged 20-60 years in outpatient visits.

Prevalence and Healthcare Costs and Resource Use

Prevalence

The prevalence of GW was estimated from physicians' daily logs of patients seen over a two-week period. The number of new or existing GW cases was captured during consultations recorded in physicians' daily logs. Physicians collected information for 2 weeks; data collection throughout the country spanned a maximum of 8 weeks. Previously diagnosed GW patients who sought medical care for another reason were not considered.

In physician practices, GW prevalence was calculated using the number of new or existing GW cases divided by the total number of patients seen during the two-week study period. Prevalence was estimated for all patients; stratified prevalence estimates by physician specialty, age group, and gender were also calculated. GW prevalence was estimated according to the underlying sample population to provide a national-level prevalence estimate. National-level prevalence was estimated based on the estimated prevalence for each specialty and the distribution of GW patients seeking for attendance between specialties. The proportion of GW

patients seeing each specialty was calculated based on the following formula: $Gi = (Si * Di) / (\Sigma i = 1 \text{ to } 4\ Si * Di)$. Where, *S* is the number of physicians of specific specialty in the country (obtained from a database maintained by IMS consulting), *D* is the mean number of GW patients (based on two-week daily logs) seen by the specific specialist, and *i* is the specialty (gynecology, urology, primary care/family medicine, dermatology). The proportion of patients seeing each specialist was used in the following formula to derive weights applied to patients included in the study database and then used to derive a national-level prevalence estimate: $W = (Gi * nT) / (ni)$, where *Gi* is the proportion of GW patients at a national level visiting each specialist, *nT* is the total number of patients counted in the study, and *ni* is the total number of patients counted in the study for a specific specialty.

Healthcare Costs and Resource Use

Referral patterns, resource use, and costs for GW patients were captured through a 30-minute face-to-face physician survey from July 26, 2011 to September 27, 2012. This survey was conducted after the physicians' daily logs. The survey included questions related to resource use as part of the usual course of diagnoses, treatment (treatments and procedures performed in-office and topical treatments applied in-office or prescribed at home), and follow-up care (medical visits, emergency room [ER] visits, hospitalizations) of typical GW patients in their practice. Survey questions were included to determine patient referral patterns in the practice, from PCPs to specialists and between specialists. Referral patterns were assessed from the physician survey, including the percentage of patients consulted directly by PCP, DERM, or URO, and the percentage of patients referred from another physician.

Costs were also reported by physician specialty in 2014 US dollars, converted from the South Korean Won (KRW). The costs per unit of healthcare service were collected from the

HIRA Service, and unit cost was applied to the described health resources. For instance, if a particular treatment procedure cost approximately KRW ₩100 and on average, only 50% of patients actually received that treatment, then the cost for a typical patient would be KRW ₩50. Costs were summed across healthcare units to compute the total mean cost of GW for a typical patient.

Statistical Analysis

All study outcomes were summarized descriptively. P-values were calculated using t-tests or the Mann-Whitney U-test for continuous variables; Chi-square tests or Fisher Exact tests were used for binary or categorical variables.

GW prevalence of new or existing cases was calculated by physician specialty type, based on the number of new or existing cases observed, divided by the total number of patients seen during the two-week study period. The weighted prevalence was calculated based on the proportion of GW patients at the national level seen by each specialist type, multiplied by the total number of patients in the study, and divided by the total number of patients seen by each specific specialty. Prevalence was calculated using normal distribution, due to the large number of patients recorded in the daily logs.[14]

Prevalence estimates were stratified by region, age group, gender, and physician specialty. Number, mean, and 95% confidence intervals (CIs) were reported. Each physician specialty type reported the number and percentage of new or existing patients with GW. Recurrent and resistant cases for existing GW patients were also reported.

Referral patterns for GW patients were reported descriptively for the last 20 male and last 20 female patients. Reported were number, mean, standard deviation (SD), median, and

minimum/maximum percentage of patients who directly consulted with, or were referred by, each physician specialty type. Healthcare resource use was reported and compared across physician specialties. P-values were calculated using Mann-Whitney U tests.

RESULTS

Prevalence

A total of 200 physicians participated in the study (Table 1).

Table 1. Participating Physicians by Region and GW Cases by Specialty in South Korea[a]

Region	PCP (n=50)	DERM (n=35)	OB/GYN (n=65)	URO (n=50)	Overall (n=200)
Busan	6 (12.0%)	5 (14.3%)	9 (13.8%)	9 (18.0%)	29 (14.5%)
Daegu	3 (6.0%)	3 (8.6%)	8 (12.3%)	7 (14.0%)	21 (10.5%)
Daejeon	2 (4.0%)	2 (5.7%)	5 (7.7%)	4 (8.0%)	13 (6.5%)
Gwangju	2 (4.0%)	3 (8.6%)	4 (6.2%)	4 (8.0%)	13 (6.5%)
Seoul	37 (74.0%)	22 (62.9%)	39 (60.0%)	26 (52.0%)	124 (62.0%)
Valid n	50	35	65	50	200

GW Cases by Specialty in South Korea					
Patients with GW	7 (0.01%)	15 (0.1%)	147 (0.8%)	133 (0.8%)	302
New or existing GW					
New Case[b]	4 (57.1%)	6 (40.0%)	74 (50.3%)	78 (58.6%)	163 (53.6%)
Existing Case[c]	3 (42.9%)	9 (60.0%)	73 (49.7%)	55 (41.4%)	140 (46.3%)
Valid n Patients	7	15	147	133	302
Existing Cases					
Recurrent Case[d]	3 (100.0%)	3 (33.3%)	43 (58.9%)	29 (52.7%)	78 (55.7%)
Resistant Case[e]		6 (66.7%)	30 (41.1%)	26 (47.3%)	62 (44.3%)
Valid n Patients	3	9	73	55	140

[a]Physician percentages were calculated over the corresponding valid n.

[b]New Case: GW not diagnosed previously by yourself or another physician.

[c]Existing Case: GW diagnosed previously by yourself or another physician.

[d]Recurrent Case: GW where previous episodes had resolved with treatment.

[e]Resistant Case: GW where previous episodes had not resolved with treatment.

GW: genital warts, PCP: primary care physician; DERM: dermatology; OB/GYN: obstetrics/gynecology; URO: urology

Regional differences ($p<0.05$) ranged from a high prevalence of GW in Gwangju followed by Busan. The lowest prevalence was observed in Daejeon (Table 2).

Table 2. GW Prevalence in Male and Female Patients in South Korea by Region (Weighted Data)

Region	All Patients[a] (n)	Patients with Identified GW Status y/n[b] (n)	Patients with New or Existing GW (n)	Patients with New or Existing GW (%, 95% CI)[c]
Busan	11,214	11,214	60	0.97 (0.83; 1.11)
Daegu	6,773	6,773	26	0.63 (0.46; 0.80)
Daejeon	4,078	4,078	3	0.62 (0.42; 0.82)
Gwangju	5,030	5,030	44	1.51 (1.32; 1.70)
Seoul	44,560	44,560	169	0.74 (0.68; 0.80)
Overall	71,655	71,655	302	0.80 (0.75; 0.85)

[a]'All patients' includes all patients reported for the corresponding country.

[b]Includes those patients with available information (excluding missing values) about GW status (Yes/No).

[c]Percentage and 95% CI calculated taking into account the number of patients with identified GW status; weighted data.

GW: genital warts; CI: confidence interval

GW prevalence varied by age (Figure 1). There was a higher prevalence among men than among women. For men and women, GW prevalence generally decreased as age increased (Figure 1). URO and OB/GYN physicians reported a higher prevalence of GW patients. Few GW patients were treated by a PCP or DERM (Figure 2). The frequency of existing GW was slightly higher among patients treated by a DERM than in the remaining specialties. The percentage of patients who were resistant to GW treatment differed in PCP consultations and DERM consultations (Table 1).

Referral Patterns, Healthcare Resource Use and Costs

Male Patients

Few patients treated by participating physicians were referred by other physicians. The mean number of reported visits was similar across physician specialties (Table 3).

Table 3. Number of Office Visits during a GW Episode and Number of Hospital and ER Visits for Male and Female Patients in South Korea

	PCP (n=50)	DERM (n=35)	URO (n=50)	Overall[a] (n=85)	p-value
Male Patients					
# Office Visits					
Mean	2.71	3.33	2.63	2.91	0.0355
SD	1.30	1.65	1.20	1.43	
Median	3.0	3.0	3.0	3.0	
Minimum	1.0	1.0	1.0	1.0	

	PCP (n=50)	DERM (n=35)	URO (n=50)	Overall[a] (n=85)	p-value
Maximum	7.0	8.0	6.0	8.0	
Valid n	28	33	49	82	
# Hospital or ER Visits					
Mean	0.81	1.03	0.35	0.62	0.1662
SD	1.33	2.08	0.97	1.53	
Median	0	0	0	0.0	
Minimum	0	0	0	0.0	
Maximum	4.0	8.0	5.0	8.0	
Valid n	21	30	46	76	
	PCP (n=50)	**DERM (n=35)**	**OB/GYN (n=65)**	**Overall* (n=100)**	**p-value[b]**
Female Patients					
# Office Visits					
Mean	3.17	4.04	3.71	3.81	0.9966
SD	1.69	3.46	1.73	2.37	
Median	3.0	3.5	3.0	3.0	
Minimum	1.0	1.0	1.0	1.0	
Maximum	7.0	20.0	10.0	20.0	
Valid n	18	28	65	93	
# Hospital or ER Visits					
Mean	0.57	0.92	0.41	0.56	0.1512

	PCP (n=50)	DERM (n=35)	URO (n=50)	Overall[a] (n=85)	p-value
SD	1.16	1.75	1.13	1.36	
Median	0.0	0.0	0.0	0.0	
Minimum	0.0	0.0	0.0	0.0	
Maximum	4.0	5.0	5.0	5.0	
Valid n	14	25	59	84	

[a]The overall column does not include PCP records.

[b]Mann-Whitney U test (does not include PCP records)

GW: genital warts; ER: emergency room; DERM: dermatology; OBGYN: obstetrics/gynecology; URO: urology; SD: standard deviation

The primary diagnostic technique was clinical diagnosis by visual examination. URO used the HPV polymerase chain reaction (PCR) test in 12.7% of patients, biopsy in 7.3%, and urethoscopy/meatoscopy (depending on the anatomical site) in 3.0%. Based on the last 20 male patients with GW, participating physicians reported the use of in-office treatments or procedures. Physicians used laser surgery in 46.4% of patients, followed by electrosurgery (42.5%), trichloroacetic acid (11.5%), and cryotherapy (9.0%). Cryotherapy was more frequently used by DERM (50.6%, 18.5% of patients) than by PCP (40.7%, 5.4% of patients) or URO (43.6%, 2.7% of patients; $p<0.001$). Electrosurgery was more frequently used by URO (57.2%; $p<0.0010$). In-office topical medications were administered more often by DERM compared to other physicians, but the differences were not statistically significant (Figure 3).

Female Patients

The majority of female GW patients were not referred by another physician. The median number of visits reported was quite similar across physician specialties. (Table 3). Participating physicians reported the mean in-office diagnostic tools and techniques, treatments or procedures based on the last 20 female GW patients seen. Diagnostic tools and techniques used most frequently by physicians to diagnose GW among female patients included visual examination (100% of patients), followed by Pap test (18.4%), biopsy (16%), histological examination (13%), HPV PCR test (11.3%), Hybrid Capture 2 HPV DNA test (8.2%), colposcopy (7.4%), and acetic acid tests (6.7%). There were differences in the use of particular diagnostic tools and techniques. OB/GYN used most of the tests more frequently, including the Pap smear (26.38%; $p<0.001$), colposcopy (9.92%; $p=0.0430$), histological examination (17.52%; $p=0.010$), HPV PCR (16.23%; $p=0.0010$), and Hybrid Capture 2 HPV DNA Test (11.69%; $p=0.003$).

For female GW patients, electrosurgery was the procedure most frequently used by all physicians in-office (55.16%), followed by laser surgery (29.77%), trichloroacetic acid (13.01%), and cryotherapy (6.67%). Cryotherapy was administered more frequently by DERM (19.24% of patients) than by PCP (7.22%) or URO (1.23%; $p<0.001$); electrosurgery was performed more frequently by OB/GYN (64.46%) than by PCP, DERM, or URO.

During the course of treatment for a GW episode in female patients, 28.82% were prescribed imiquimod topical (Aldara) as an at-home topical medication (Figure 3). Foscamet sodium injection (250 mml, 500mml) was not reported as a treatment for female GW patients, and thus not shown for female patients in Figure 3. Imiquimod topical was used more frequently as an at-home medication compared to an in-office medication.

Healthcare Costs for Male and Female Patients

Figure 4 shows median costs associated with diagnosis and management of GW in male and female patients. Higher costs were associated with GW in female patients (median costs: US $66.29 (KRW ₩76,113) due to the significantly high costs for diagnosis, treatment procedures, and at-home medications administered by DERM or OB/GYN, compared to male patients whose median costs for GW were US $58.23 (KRW ₩66,857). In addition, statistically significant differences were observed between DERM and URO physicians for overall annual, diagnostic tool and technique, office visit, and at-home topical medication prescription costs (p-values: 0.0232, 0.0033, 0.0355 and 0.0096, respectively). Among female patients, the overall annual cost comparison of DERM and OB/GYN practices presented no statistically significant differences (p-value=0.5919). However, significant differences by physician specialty for diagnostic tools and techniques, in-office treatment and procedure costs, and topical medication prescription costs for at-home use (p-values: <0.0001, 0.0073 and 0.0037, respectively) were observed.

DISCUSSION

This cross-sectional study estimated the burden of GW in South Korea by estimating the prevalence of GW and GW-related resource use and costs among male and female patients aged 20-60 years. At the South Korean national level, the current study estimated GW prevalence at 0.99% for male patients and 0.63% for female patients, which is lower compared to those reported in the United States, Denmark, Iceland, Norway, and Sweden [15, 16] and in other studies conducted in South Korea.[17, 18] For instance, the US National Health and Nutrition Examination Survey (NHANES) found that from 1999 through 2004, 5.6% of survey respondents (aged 18-59 years) self-reported a GW diagnosis.[19] The percentage was higher in female patients (7.2%; 95% CI: 6.2%-8.4%) compared to male patients (4%; 95% CI: 3.2%-

5.0%). However, a previous study performed in Hong Kong that included 170 private doctors working in social hygiene clinics and using a similar study design to our study, estimated an overall GW prevalence rate of 0.94%, which is similar to the current study.[20] The distribution of GW differed according to gender after adjusting for age (Figure 1).

An earlier Korean study of patients visiting URO and OB/GYN clinics found that the predominant age group diagnosed with GW was 25-29 years in male patients (prevalence: 1.84%), and 30- 34 years in female patients (prevalence: 0.25%).[13] In the United States, HPV prevalence was found to be highest among women aged 20-24 years (18.5%; 95% CI: 14.9%-22.8%).[21] When examining a single gender group, the study results showed that the highest prevalence of GW was seen in male patients aged 25-29 (2.47%). The highest prevalence of GW in female patients was in ages 18-24 (1.70) and 25-29 (1.22%). These results are consistent with findings from previous studies performed in Australia, the United States, and Canada.

Results from a systematic review of GW incidence and prevalence conducted in four Nordic European countries showed a wide range of prevalence in the self-reported history of GW. In surveys of general adult populations, 0.36% (Slovenia, sexually-active, aged 18-49 years) to 12.0% (Iceland, aged 18-45 years) of women reported a lifetime history of GW.[16] The proportion of GW in male populations varied from 3.6% to 7.9% in Australia, Denmark, United Kingdom, and United States, and was 0.27% in Slovenia, from November 2004-June 2005.[20]

Differences in sexual behavior and use of different case-ascertainment methods for GW-related data may explain differences in prevalence found in these European studies compared to South Korea. In South Korea, the average age of a woman's first sexual intercourse experience is approximately 20 years,[22] compared to 16 years in the European studies. In the Kjaer, *et al*.

study,[16] GW prevalence was calculated using self-reported data, while in the current study only patients seeking healthcare were included. Therefore, the burden of GW may have been higher due to those not seeking treatment or unreported cases.

In Australia, Pirotta, *et al*. estimated an annual incidence rate of 2.19 cases of GW per 1,000 Australians, with peak incidence in women aged 20-24 years, at 8.61 cases per 1,000, and in men aged 25–29 years, at 7.40 cases per 1,000.[23] In the United States, a study by Hoy, *et al*. found that GW incidence was highest among women aged 20-24 (4.6/1,000) and men aged 25-29 (2.7/1,000), in 2004.[11] Similarly, a study conducted in Canada found that overall GW prevalence between 1998 and 2006 was higher among men than women. Data from 2006 showed that prevalence was highest among women aged 20-24 years (3.88/1,000), whereas in men, the prevalence peaked at age 25-29 years (3.69/1,000).[24]

The most common treatment options for GW are podofilox, imiquimod, surgical excision, and cryotherapy.[25] In the current study, electrosurgery was the most frequently used therapy, followed by pharmacological topical treatments in the office and at home, and other surgical procedures.

In-office treatment for GW varied by physician specialty, with cryotherapy more frequently administered by DERM than by other specialists, possibly because of expertise and access to equipment. Likewise, electrosurgery was more frequently used by URO and DERM than by PCP and OB/GYN. Imiquimod was the topical medication of choice for treatment of GW. As expected, patient referral to specialists was higher for PCP, who referred most men to URO and most women to OB/GYN. Specialists also referred patients to physicians within the same specialty (e.g., DERM referred to another DERM, etc.).

GW diagnosis and treatment for male patients was associated with overall median costs of US $58.23 (KRW ₩66,857), and US $66.29 (KRW ₩76,113) for female patients. For male patients, the highest overall costs were due to office visits (49.02%), followed by in-office treatments and procedures (33.17%), and diagnostic tools and techniques (16.34%). For female patients, most costs were office visits (61.87%), followed by diagnostic tools and techniques (30.78%), and in-office topical medications (7.35%).

The United States, France, and Canada have conducted considerable research on GW-related healthcare costs. A Canadian claims data study found that the average cost per GW episode was CaD $190 (male: CaD$ 176; female: CaD$ 207).[24] However, this study is not comparable with the South Korean study given the socioeconomic and healthcare system differences between the two countries. A more analogous study methodology and design for cost estimation was conducted in Australian sexual health clinics by Pirotta *et al*. This study showed high costs associated with GW in women (A$ 386) as compared to males (A$ 251), similar to trends found in the current study.[23]

Contributorship Statement

TSL, SKT, PKS, KY, AK, ARG, SMG, WJ, NL, and MR conceived and designed the experiments for this manuscript.

NL, MR, SKT, PKS, AK performed the experiments for this manuscript.

NL, MR analyzed the data for this manuscript.

NL, MR contributed reagents/materials/analysis tools for this manuscript.

All authors contributed to the writing of this manuscript.

Competing Interests

- T.S. Lee has no conflicts to declare.
- K. Yee was a paid contractor for Merck and Co. at the time of the study, and was an employee of Cubist Pharmaceuticals December 2014 – July 2015, which was acquired by Merck and Co. in January 2015.
- A. Kulkarni, S. Kothari-Talwar, and P.K. Singhal are employees of Merck and Co.
- S.M. Garland received Grants to her institution from the Commonwealth Department of Health for HPV genoprevalance surveillance post vaccination, Merck and Co., and Glaxo Smith Kline to perform phase 3 clinical vaccine trials: Merck to evaluate HPV in RRP post vaccination programme; CSL for HPV in cervical cancer study, and VCA for a study on the effectiveness of a public health HPV vaccine study, and a study on the associations of early onset cancers. Received speaking fees from MSD and SPMSD for work performed in her personal time. Merck and Co. paid for travel & accommodation to present at HPV Advisory board meetings.
- A.R. Giuliano is a member of Merck & CO, Inc. advisory boards. Her institution has received grants and contracts to support HPV-related research.
- N. Lara and M. Roset are employees of IMS Health, Barcelona, Spain, which is a paid consultant to Merck and Co.
- W. Ju has no conflicts to declare.

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Data Sharing Statement:

Data is property of Merck & Co. Inc., and can be accessed with permission from Merck & Co. Inc.

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Figure Legends

Figure 1. GW Prevalence in South Korea

GW: genital warts; PCP: primary care physician; OBGYN: obstetrics/gynecology; URO: urology; DERM: dermatology

Figure 2. Mean Percentage of Male and Female GW Patients using an In-Office Treatment or Procedure During Treatment for GW in South Korea

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Figure 4. Median Costs Associated With GW Diagnosis and Treatment in Male and Female Patients

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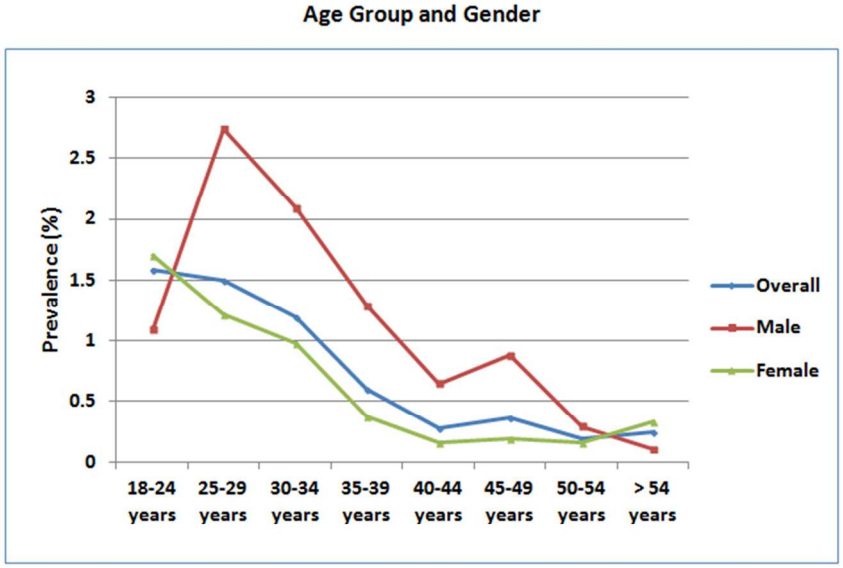

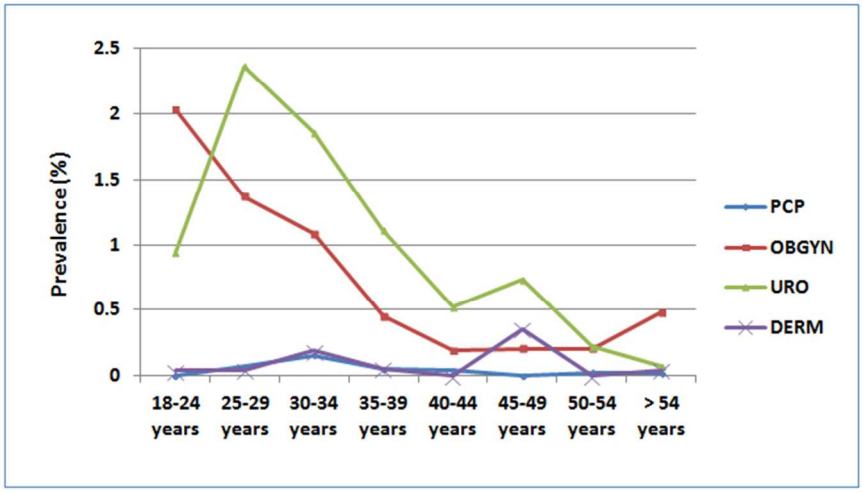

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Figure 1
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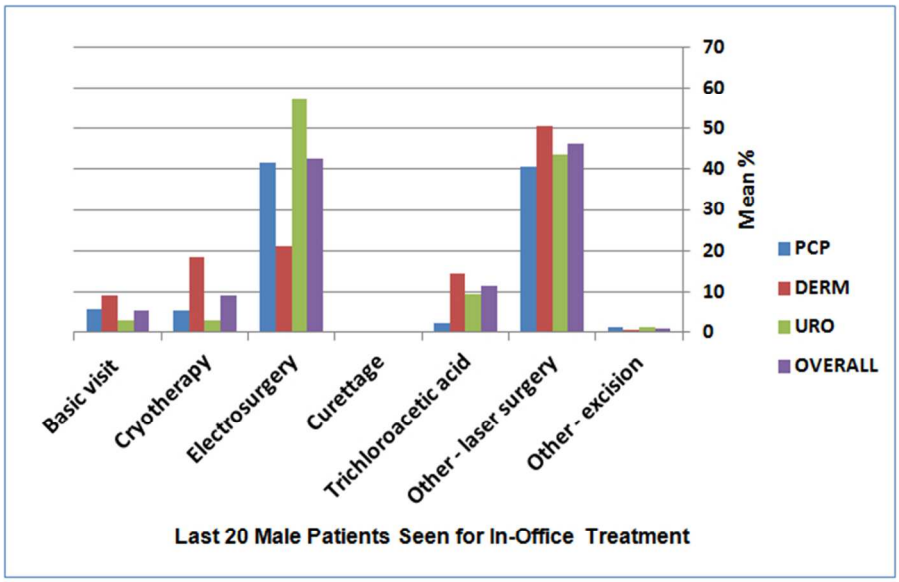

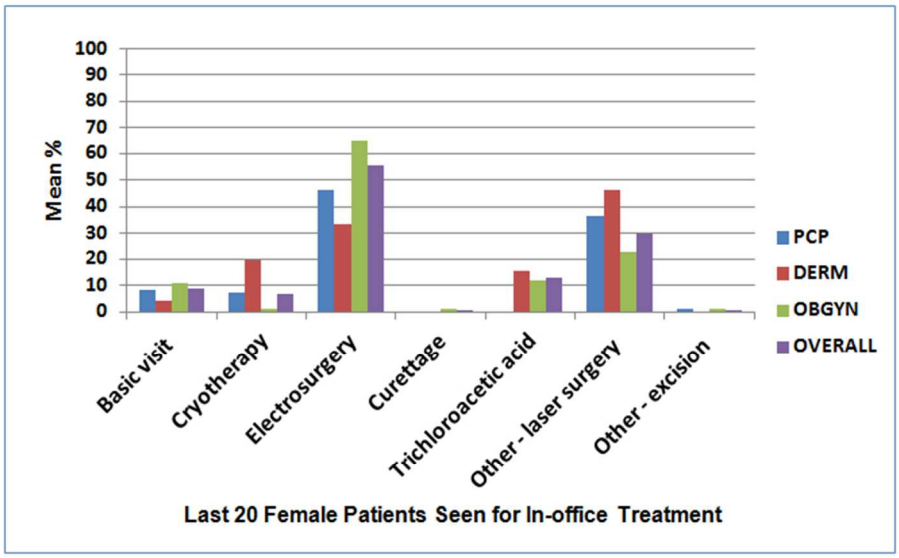

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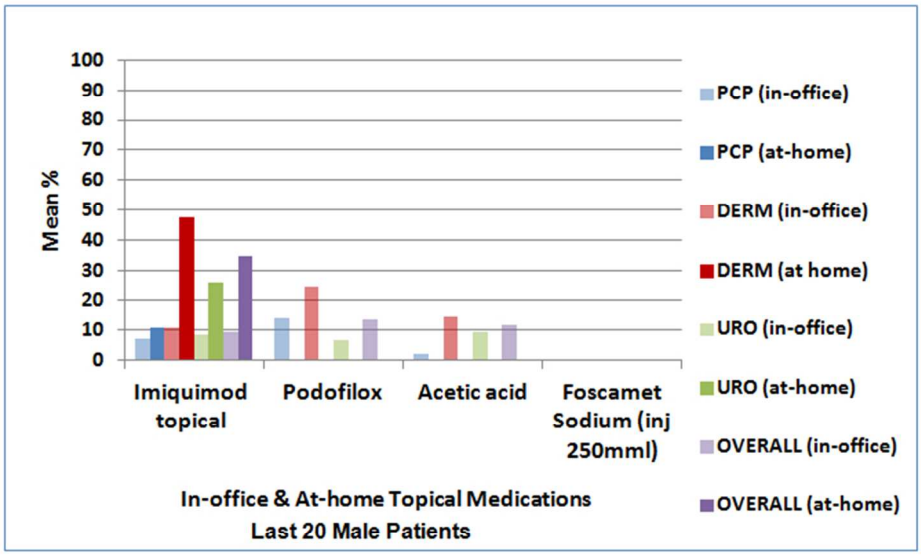

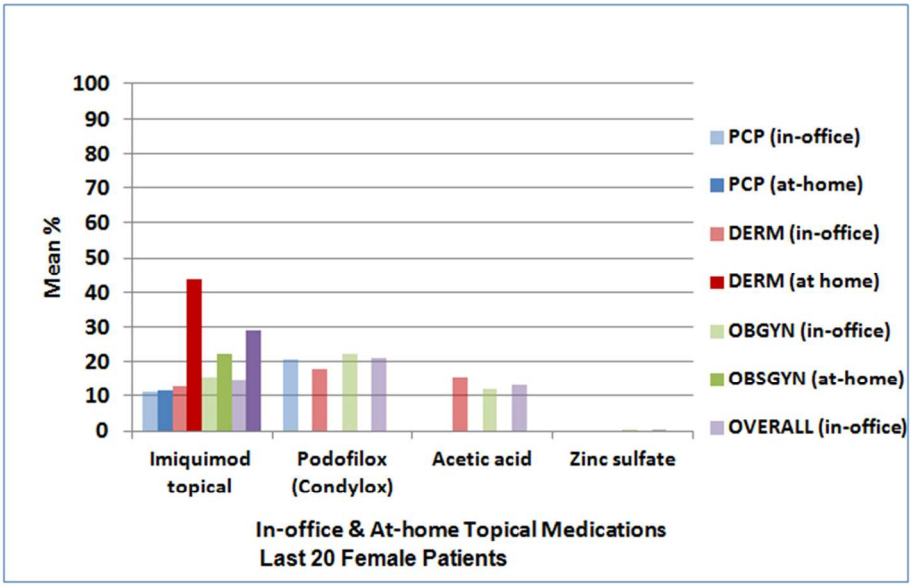

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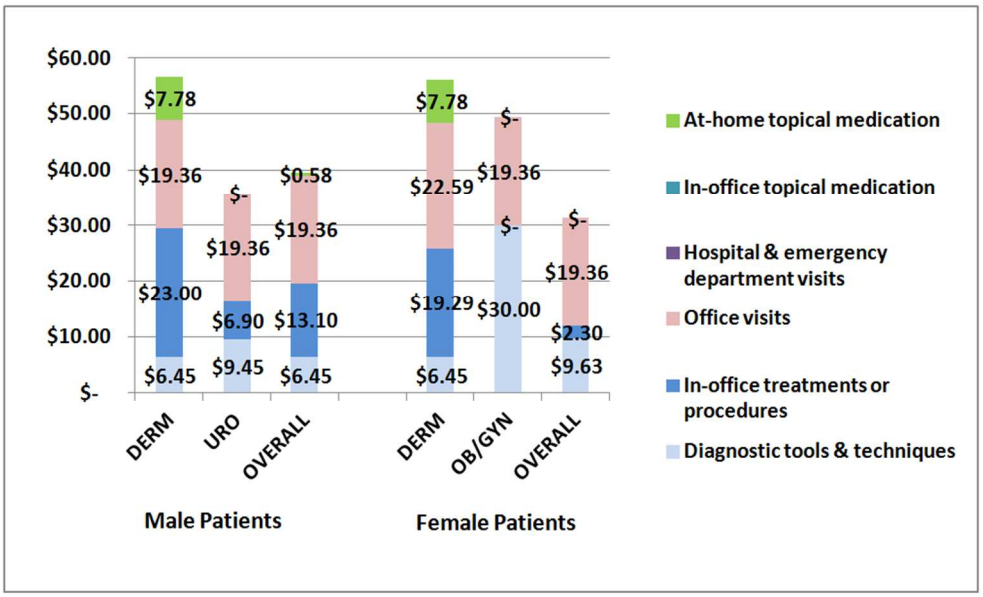

Figure 4. Median Costs Associated With GW Diagnosis and Treatment in Male and Female Patients

GW: genital warts; PCP: primary care physician; DERM: dermatology; URO: urology; OB/GYN: obstetrics/gynecology

GW: genital warts; PCP: primary care physician; DERM: dermatology; OBGYN: obstetrics/ gynecology; URO: urology; inj: injection
Figure 4
87x54mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **–Pg. 2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **– Pg. 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **–Pg. 4-5**
Objectives	3	State specific objectives, including any prespecified hypotheses – **Pg. 2**
Methods		
Study design	4	Present key elements of study design early in the paper – **Pg. 5-6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – **Pg. 2 and 7-8**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up – **N/A** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls **– N/A** *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **–Pg. 2 and 5-6**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed – **N/A** *Case-control study*—For matched studies, give matching criteria and the number of controls per case – **N/A**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable – **Pg. 6-8**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group – **Pg. 5-8**
Bias	9	Describe any efforts to address potential sources of bias – **Pg. 3**
Study size	10	Explain how the study size was arrived at – **Pg. 5-6**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why – **Pg. 6 - 8**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **– Pg. 2 and Pg. 6-8**
		(*b*) Describe any methods used to examine subgroups and interactions – **Pg. 6-8**
		(*c*) Explain how missing data were addressed – **N/A**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **–N/A** *Case-control study*—If applicable, explain how matching of cases and controls was addressed **– N/A** *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy **Pg. 5-6**
		(*e*) Describe any sensitivity analyses – **N/A**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed – **Pg 2-3 and 5-6**
		(b) Give reasons for non-participation at each stage – **Pg. 5-6**
		(c) Consider use of a flow diagram – **N/A**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – **Pg. 2, 5-6, and 9 – 16**
		(b) Indicate number of participants with missing data for each variable of interest –**N/A**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) – **N/A**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time –**N/A**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure –**N/A**
		Cross-sectional study—Report numbers of outcome events or summary measures – **Pg. 9-16**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – **Pg. 11, 16**.
		(*b*) Report category boundaries when continuous variables were categorized – **N/A**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. – **N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses – **Pg 6-8, 9-16**
Discussion		
Key results	18	Summarise key results with reference to study objectives – **Pg. 11 – 16**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – **Pg. 3**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence – **Pg. 16 – 19**
Generalisability	21	Discuss the generalisability (external validity) of the study results – **Pg. 16 – 19**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based – **Pg. 21**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

A Cross Sectional Study Estimating the Burden of Illness Related to Genital Warts in South Korea

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Obstetrics and gynaecology, Sexual health
Keywords:	GYNAECOLOGY, INFECTIOUS DISEASES, OBSTETRICS

Title: A Cross Sectional Study Estimating the Burden of Illness Related to Genital Warts in South Korea

Running Head: Cross Sectional Study: Estimating the Burden of Genital Warts in South Korea

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ABSTRACT

Objectives: Estimate the prevalence of genital warts (GW) and GW-related healthcare resource use and costs among male and female patients seeking treatment in clinics in South Korea.

Design: To estimate GW prevalence, physicians in 5 major South Korean regions recorded daily logs of patients (N=71,655) seeking care between July 26 and September 27, 2011. Overall prevalence estimates (and 95% CIs) were weighted by the estimated number of physicians in each specialty and the estimated proportion of total patients visiting each specialist type. Healthcare resource use was compared among different specialties. Corresponding p-values were calculated using Mann-Whitney U tests.

Setting: The database covers 5,098 clinics for five major regions in South Korea: Seoul, Busan, Daegu, Kwangju, and Daejeon.

Participants: Primary care physicians (PCPs; general practice/family medicine), OB/GYNs, UROs, and dermatologists (DERMs) with 2-30 years' experience).

Results: The estimated overall GW prevalence was 0.7% (95% confidence interval [CI]: 0.7-0.8%). Among women, GW prevalence was 0.6% (95% CI: 0.6-0.7%); among men prevalence was 1.0% (95% CI: 0.9-1.0%), peaking among patients aged 18-24 years. Median costs for GW diagnosis and treatment for male patients were US $58.2 (South Korean Won [KRW] ₩ 66,857) and US $66.3 (KRW ₩ 76,113) for female patients.

Conclusions: The estimated overall GW prevalence in South Korea was 0.7% and was higher for male patients. The overall median costs associated with a GW episode were higher for female patients than for male patients.

Abstract word count: 232

Keywords: genital warts, healthcare resource use, South Korea

Article Summary:

- Physicians in 5 major South Korean regions recorded daily logs of patients (N=71,655).
- The prevalence of GW was estimated from physicians' daily logs of patients seen over a 2-week period.
- Referral patterns, resource use, and costs for GW patients were captured through a 30-minute face-to-face physician survey from July 26, 2011 to September 27, 2012.
- The numbers of new, existing, recurrent, and resistant GW cases were calculated.
- Prevalence estimates were stratified by region, age group, sex, and physician specialty.

Strengths and Limitations:

Strengths of this survey include the limited existing research on GW prevalence and cost in South Korea and the presence of data across multiple physician specialties and geographic regions.

Limitations for this study include participating physicians having an increased likelihood to treat GW patients, possibly resulting in an overestimation of GW in South Korea. GW prevalence was not estimated from a random sample of physicians. National prevalence estimates were based on the physician population available from the IMS database, which may not include all physicians in South Korea. GW patients who did not seek healthcare treatment were not included. Potential bias may exist, related to the information source (physician survey) and the direction of bias is unknown.

BACKGROUND

Human papillomavirus (HPV) infections are the etiologic agents of genital warts (GW) and squamous intraepithelial lesions.[1] HPV is one of the most frequent sexually-transmitted viral infections[2-3] and has more than 130 identified virus types.[4] HPV 6 and 11 alone are estimated to cause approximately 90% of GW infections.[5] GW are highly infectious and nearly 65% of individuals with an infected partner develop lesions within 3 weeks-8 months from the first contact.[3,5] HPV prevalence varies by age and is higher among women and more common for young women with a new sexual partner.[6] Research suggests that an estimated 6.2 million new infections occur annually in individuals aged 14-44 years in the United States.

Data on national GW incidence by country are limited, and prevalence estimates by country range widely from 1.4% (Spain)[7] to 25.6% (Nigeria).[8, 9] In a recent systematic review undertaken to determine worldwide GW incidence and prevalence (from published data, January 2001-January 2012), GW incidence differed in regional distributions from 101-205, 118-170, and 204 new GW cases per 100,000 people in North America, Europe, and Asia, respectively. Age-specific GW incidence peaked for male patients aged 25-29 years and female patients 20-24 years, and remained significant in patients aged 30-45 years.[3]

Available GW treatments include patient-applied (home-based) chemicals (podofilox, imiquimod), provider-administered (office-based) chemicals (podophyllin, trichloracetic acid, interferon), and ablative treatment (cryotherapy, surgery, laser).[10] GW treatment and management can result in significant direct and indirect costs, and can cause a considerable financial burden, involving frequent physician office visits, medication application, and mechanical removal of warts. A study assessing incidence and economic burden on US commercially-insured patients reported estimated costs at $760 per 1,000 individuals in the

general population in 2004, with total costs exceeding $220 million.[11] Another study evaluating the economic burden of GW in Belgium, found similar conclusions related to overall costs. The estimated 7,989 annual number of diagnosed GW patients led to an estimated annual cost of €2.53 million.[12]

To date, there has been little research in South Korea to assess GW incidence and prevalence. A study conducted in South Korea among patients visiting urology (URO) and obstetrics/gynecology (OB/GYN) clinics observed a GW prevalence of 0.4% with a higher prevalence among young patients. Among patients with GW, 21% reported to have suffered a GW recurrence.[13] As such, the burden of GW may have a larger economic impact on society than previously estimated. Given the lack of available data in South Korea, the current study was designed to estimate GW prevalence in physician practices, and GW-related healthcare resource use and costs in South Korea among male and female patients aged 20-60 years.

METHODS

Study Design

This was a cross-sectional study conducted via survey in the major regions of South Korea to estimate GW prevalence in physician practices, and GW-related healthcare resource use and costs in South Korea among male and female patients. In addition, patients diagnosed with GW were stratified as new, existing, recurrent, and resistant cases. The study protocol and list of participating clinics were submitted to the participant hospitals' Institutional Review Boards (IRBs). The study protocol was reviewed and approved by the National Evidence-based Health Care Collaborating Agency (NECA), the SMG-SNU University Medical Center, and the Ewha Women's University Mokdong Hospital ethics committees. No confidential patient-level data was collected for this study.

Inclusion and Exclusion Criteria

Participating Physicians

Participating physicians were identified through the Korean Intercontinental Marketing Services (KR IMS) database, which contains nationwide clinics published by the Health Insurance Review and Assessment (HIRA) Service. The database covers 5,098 clinics for 5 targeted specialties in 5 major regions in South Korea: Seoul, Busan, Daegu, Kwangju, and Daejeon. Enrollment in the National Insurance System is mandatory for all clinics, and are monitored by the HIRA in South Korea.

Physicians included in this study:

a) provided informed consent to participate and were specialists, including primary care physicians (PCPs); general practice/family medicine), OB/GYNs, UROs, and dermatologists (DERMs) with 2-30 years' experience);

b) devoted at least 30% of their time seeing and treating patients in outpatient visits, 3 or more work days per week (as opposed to inpatient surgeries, teaching, or other activities);

c) treated ≥75 patients in outpatient visits in a typical week; and

d) treated ≥50% of patients aged 20-60 years in outpatient visits.

Healthcare Costs and Resource Use

Referral patterns, resource use, and costs for GW patients were captured through a 30-minute face-to-face physician survey from July 26, 2011 to September 27, 2012. This survey was conducted after the physicians' daily logs. The survey included questions related to resource use as part of the usual course of diagnoses, treatment (treatments and procedures performed in-

office and topical treatments applied in-office or prescribed at home), and follow-up care (medical visits, emergency room [ER] visits, hospitalizations) of typical GW patients in their practice. Survey questions were included to determine patient referral patterns in the practice, from PCPs to specialists and between specialists. Referral patterns were assessed from the physician survey, including the percentage of patients consulted directly by PCP, DERM, or URO, and the percentage of patients referred from another physician.

Costs were also reported by physician specialty in 2014 US dollars, converted from the South Korean Won (KRW). The costs per unit of healthcare service were collected from the HIRA Service, and unit cost was applied to the described health resources. For instance, if a particular treatment procedure cost approximately KRW ₩100 and on average, only 50% of patients actually received that treatment, then the cost for a typical patient would be KRW ₩50. Costs were summed across healthcare units to compute the total mean cost of GW for a typical patient.

Statistical Analysis

All study outcomes were summarized descriptively. P-values were calculated for comparison between the groups (ie, region, age, sex, and physician specialty) using t-tests or the Mann-Whitney U-test for continuous variables; Chi-square tests or Fisher Exact tests were used for binary or categorical variables.

GW prevalence of new or existing cases was calculated by physician specialty type, based on the number of new or existing cases observed, divided by the total number of patients who were seen during the 2-week study period. The weighted prevalence was calculated based on the proportion of GW patients at the national level seen by each specialist type, multiplied by the total number of patients in the study, and divided by the total number of patients seen by each

specific specialty. Prevalence was calculated using normal distribution, due to the large number of patients recorded in the daily logs. [14]

Prevalence estimates were stratified by age group, sex, and physician specialty. Number, mean, and 95% confidence intervals (CIs) were reported. Each physician specialty type reported the number and percentage of new or existing GW patients. Recurrent and resistant cases for existing GW patients were also reported.

RESULTS

Prevalence

A total of 200 physicians participated in the study (Table 1).

Table 1. Participating Physicians by Region and GW Cases by Specialty in South Korea[a]

Participating Physicians by Region in South Korea					
Region	**PCP (n=50)**	**DERM (n=35)**	**OB/GYN (n=65)**	**URO (n=50)**	**Overall (n=200)**
Busan	6 (12.0%)	5 (14.3%)	9 (13.8%)	9 (18.0%)	29 (14.5%)
Daegu	3 (6.0%)	3 (8.6%)	8 (12.3%)	7 (14.0%)	21 (10.5%)
Daejeon	2 (4.0%)	2 (5.7%)	5 (7.7%)	4 (8.0%)	13 (6.5%)
Gwangju	2 (4.0%)	3 (8.6%)	4 (6.2%)	4 (8.0%)	13 (6.5%)
Seoul	37 (74.0%)	22 (62.9%)	39 (60.0%)	26 (52.0%)	124 (62.0%)
Total Patients	50	35	65	50	200
GW Cases by Specialty in South Korea					
Patients with GW	7 (0.01%)	15 (0.1%)	147 (0.8%)	133 (0.8%)	302
New or existing GW					
New Case[b]	4 (57.1%)	6 (40.0%)	74 (50.3%)	78 (58.6%)	163 (53.6%)
Existing Case[c]	3 (42.9%)	9 (60.0%)	73 (49.7%)	55 (41.4%)	140 (46.3%)
Valid n Patients	7	15	147	133	302
Existing Cases					
Recurrent Case[d]	3 (100.0%)	3 (33.3%)	43 (58.9%)	29 (52.7%)	78 (55.7%)
Resistant Case[e]		6 (66.7%)	30 (41.1%)	26 (47.3%)	62 (44.3%)
Total Patients	3	9	73	55	140

[a] Physician percentages were calculated over the corresponding valid n.

[b]New Case: GW not diagnosed previously by yourself or another physician.

[c] Existing Case: GW diagnosed previously by yourself or another physician.

[d]Recurrent Case: GW where previous episodes resolved with treatment.

[e]Resistant Case: GW where previous episodes were not resolved with treatment.

DERM: dermatology; GW: genital warts; OB/GYN: obstetrics/gynecology; PCP: primary care physician; URO: urology

Regional differences ($p<0.05$) ranged from a high prevalence of GW in Gwangju followed by Busan. The lowest prevalence was observed in Daejeon (Table 2).

Table 2. GW Prevalence in Male and Female Patients in South Korea by Region (Weighted Data)

Region	All Patients[a] (n)	Average Number of Patients Per Physician (n)	Patients with New or Existing GW (n)	Patients with New or Existing GW (%, 95% CI)[b]
Busan	11,214	387	60	1.0 (0.8; 1.1)
Daegu	6,773	322	26	0.6 (0.5; 0.8)
Daejeon	4,078	314	3	0.6 (0.4; 0.8)
Gwangju	5,030	387	44	1.5 (1.3; 1.7)
Seoul	44,560	359	169	0.7 (0.7; 0.8)
Overall	71,655	358	302	0.8 (0.8; 0.9)

[a]'All patients' includes all patients reported for the corresponding region.

[b]Percentage and 95% confidence intervals were calculated, accounting for the number of patients with identified genital wart status; weighted data.

CI: confidence interval; GW: genital warts

GW prevalence varied by age (Figure 1). There was a higher prevalence among men than among women. For men and women, GW prevalence generally decreased as age increased (Figure 1). URO and OB/GYN physicians reported a higher prevalence of GW patients. Few GW patients were treated by a PCP or DERM (Figure 2). The frequency of existing GW was slightly higher among patients treated by a DERM than in the remaining specialties. The percentage of patients who were resistant to GW treatment differed in PCP consultations and DERM consultations (Table 1).

Referral Patterns, Healthcare Resource Use and Costs

Male Patients

Few patients treated by participating physicians were referred by other physicians. The mean number of reported visits was similar across physician specialties (Table 3).

Table 3. Number of Office Visits during a GW Episode and Number of Hospital and ER Visits for Male and Female Patients

	PCP (n=50)	DERM (n=35)	URO (n=50)	Overall (n=85)	p-value
Male Patients					
# Clinic Visits					
Mean (SD) (Range)	2.7 (1.3) (1.0-7.0)	3.3 (1.7) (1.0-8.0)	2.6 (1.20) (1.0-6.0)	2.9(1.4) (1.0-8.0)	0.0355[b]
Valid n	28	33	49	82	
# Hospital or ER Visits					
Mean (SD) (Range)	0.8 (1.3) (0.0-4.0)	3.3 (2.1) (0.0-8.0)	0.4 (1.0) (0.0-5.0)	0.6(1.5) (0.0-8.0)	0.1662[b]
Valid n	21	30	46	76	
	PCP (n=50)	**DERM (n=35)**	**OB/GYN (n=65)**	**Overall* (n=100)**	**p-value[b]**
Female Patients					
# Clinic Visits					
Mean (SD) (Range)	3.2 (1.7) (1.0-7.0)	4.0 (3.5) (1.0-20.0)	3.7 (1.7) (1.0-10.0)	3.8 (2.8) (1.0-20.0)	0.9966[b]
Valid n	18	28	65	93	
# Hospital or ER Visits					
Mean (SD) (Range)	0.6 (1.2) (0.0-4.0)	0.9 (1.8) (0.0-5.0)	0.4 (1.1) (0.0-5.0)	0.6 (1.4) (0.0-5.0)	0.1512[b]
Valid n	14	25	59	84	

[a]The overall column does not include Primary Care Physician records.

[b]Mann-Whitney U test (does not include Primary Care Physician records)

DERM: dermatology; ER: emergency room; GW: genital warts; OBGYN: obstetrics/gynecology; SD: standard deviation; URO: urology

The primary diagnostic technique was visual examination. URO used the HPV polymerase chain reaction (PCR) test in 12.7% of patients, biopsy in 7.3%, and urethoscopy/meatoscopy (depending on the anatomical site) in 3.0%. Based on the feedback from the last 20 male patients with GW, participating physicians reported the use of in-office treatments or procedures. Physicians used laser surgery in 46.4% of patients, followed by electrosurgery (42.5%), trichloroacetic acid (11.5%), and cryotherapy (9.0%). Cryotherapy was more frequently used by DERM (18.5%) than by PCP (5.4%) or URO (2.7%; $p<0.001$). Electrosurgery was more frequently used by URO (57.2%; $p<0.001$) compared to DERM and PCP. In-office topical medications were administered more often by DERM compared to other physicians, but the differences were not statistically significant (Figure 2).

Female Patients

The majority of female GW patients were not referred by another physician. The median number of visits reported was quite similar across physician specialties (Table 3). Participating physicians reported the mean in-office diagnostic tools and techniques, treatments or procedures based on the last 20 female GW patients who sought treatment. Diagnostic tools and techniques used most frequently by physicians to diagnose GW among female patients included visual examination (100% of patients), followed by Pap test (18.4%), biopsy (16%), histological examination (13%), HPV PCR test (11.3%), Hybrid Capture 2 HPV DNA test (8.2%), colposcopy (7.4%), and acetic acid tests (6.7%). There were differences in the use of particular

diagnostic tools and techniques. OB/GYN used most of the tests more frequently than DERM, including the Pap smear (26.4%; p<0.001), colposcopy (9.9%; p=0.0430), histological examination (17.5%; p=0.0100), HPV PCR (16.2%; p=0.0010), and Hybrid Capture 2 HPV DNA Test (11.7%; p=0.003).

For female GW patients, electrosurgery was the procedure most frequently used by all physicians in-office (55.2%), followed by laser surgery (29.8%), trichloroacetic acid (13.0%), and cryotherapy (6.7%). Cryotherapy was administered more frequently by DERM (19.2% of patients) than by PCP (7.2%) or URO (1.2%; p<0.001); electrosurgery was performed more frequently by OB/GYN (64.5%) than by PCP, DERM, or URO.

During the course of treatment for a GW episode in female patients, 28.8% were prescribed imiquimod topical (Aldara) as an at-home topical medication (Figure 3). Foscamet sodium injection (250 mml, 500mml) was not reported as a treatment for female GW patients, and thus not shown for female patients in Figure 3. Imiquimod topical was used more frequently as an at-home medication compared to an in-office medication.

Healthcare Costs for Male and Female Patients

Figure 4 shows median costs associated with diagnosis and management of GW in male and female patients. Higher costs were associated with GW in female patients (median costs: US $66.3 (KRW ₩76,113) due to the significantly high costs for diagnosis, treatment procedures, and at-home medications administered by DERM or OB/GYN, compared to male patients whose median costs for GW were US $58.2 (KRW ₩66,857). In addition, statistically significant differences were observed between DERM and URO physicians for overall annual (p-values=0.0232), diagnostic tool and technique (p-values=0.0033), office visit (p-values=0.0355), and at-home topical medication prescription costs (p-values=0.0096). Among female patients,

the overall annual cost comparison of DERM and OB/GYN practices presented no statistically significant differences (p-value=0.5919). However, significant differences by physician specialty for diagnostic tools and techniques (p-value<0.0001), in-office treatment and procedure costs (p-values=0.0073), and topical medication prescription costs for at-home use (p-values=0.0037) were observed.

DISCUSSION

This cross-sectional study estimated the burden of GW in South Korea by estimating the prevalence of GW and GW-related resource use and costs among male and female patients aged 20-60 years. At the South Korean national level, the current study estimated GW prevalence at 1.0% for male, and 0.6% for female patients, which is lower compared to those reported in the United States, Denmark, Iceland, Norway, Sweden [15, 16] and in other studies conducted in South Korea.[17, 18] For instance, the US National Health and Nutrition Examination Survey (NHANES) found that from 1999 through 2004, 5.6% of survey respondents (aged 18-59 years) self-reported a GW diagnosis.[19] The percentage was higher among female patients 7.2% compared to male patients 4%.[19] However, a previous study performed in Hong Kong that used a similar study design, estimated an overall GW prevalence rate of 0.9%, [20] which is similar to that observed in the current study, which ranged from 0.3-1.7% (Figure1).

An earlier Korean study of patients visiting URO and OB/GYN clinics found that the predominant age for those diagnosed with GW was 25-29 years among male patients (prevalence: 1.8%) which is similar to that observed among the male population in our study. Also, in the earlier Korean study, the highest prevalence in the female population was among those aged 30-34 years (prevalence: 0.3%) [13], which differs from our study results: The highest prevalence of GW was found among female patients aged 18-24 years (1.2 %). A recent

US study showed that HPV prevalence was found to be highest among women aged 20-24 years [21], as observed in this study.

Results from a systematic review of GW incidence and prevalence conducted in 4 Nordic European countries showed a wide range of prevalence in the self-reported history of GW. In surveys of general adult populations, 0.4% (Slovenia, sexually-active, aged 18-49 years) to 12.0% (Iceland, aged 18-45 years) of women reported a lifetime history of GW. [16] The proportion of GW in male populations varied from 3.6% to 7.9% in Australia, Denmark, United Kingdom, and United States, and was 0.3% in Slovenia, from November 2004-June 2005. [20] Also, results from a recent study of the Czech Republic population showed rising incidence of GW, with a 5.8% prevalence rate among patients aged 16-55 years. [22]

Differences in sexual behavior and use of different case-ascertainment methods for GW-related data may explain differences in prevalence found in these European studies compared to South Korea. In South Korea, the average age of a woman's first sexual intercourse experience is approximately 20 years, [23] compared to 16 years in the European studies. In the Kjaer, *et al*. study, [16] GW prevalence was calculated using self-reported data, while in the current study only patients seeking healthcare were included. Therefore, the burden of GW results may have been higher due to those not seeking treatment or unreported cases.

In Australia, Pirotta, *et al*. estimated an annual incidence rate of 2.2 cases of GW per 1,000 Australians, with peak incidence in women aged 20-24 years, at 8.6 cases per 1,000, and in men aged 25–29 years, at 7.4 cases per 1,000.[24] In the United States, a study by Hoy, *et al*. found that GW incidence was highest among women aged 20-24 (4.6/1,000) and men aged 25-29 (2.7/1,000), in 2004.[11] Similarly, a study conducted in Canada found that overall GW prevalence between 1998 and 2006 was higher among men than women. Data from 2006 showed

that prevalence was highest among women aged 20-24 years (3.9/1,000), whereas in men, the prevalence peaked at age 25-29 years (3.7/1,000).[25]

The most common treatment options for GW are podofilox, imiquimod, surgical excision, and cryotherapy.[26] In the current study, electrosurgery was the most frequently used therapy, followed by pharmacological topical treatments in the office and at home, and other surgical procedures.

In-office treatment for GW varied by physician specialty. Cryotherapy was more frequently administered by DERM than by other specialists, possibly because of expertise and access to equipment. Likewise, electrosurgery was more frequently used by URO and DERM than by PCP and OB/GYN. Imiquimod was the topical medication of choice for treatment of GW. As expected, patient referral to specialists was higher for PCP, who referred most men to URO and most women to OB/GYN. Specialists also referred patients to physicians within the same specialty (eg, DERM referred to another DERM, etc.).

GW diagnosis and treatment for male patients was associated with overall median costs of US $58.2 (KRW ₩66,857), and US $66.3 (KRW ₩76,113) for female patients. For male patients, the highest overall costs were due to office visits (49.0%), followed by in-office treatments and procedures (33.2%), and diagnostic tools and techniques (16.3%). For female patients, most costs were related to office visits (61.9%), followed by diagnostic tools and techniques (30.8%), and in-office topical medications (7.4%).

The United States, [27] Italy, [28] and Canada [25] have conducted considerable research on GW-related healthcare costs. A Canadian claims data study found that the average cost per GW episode was CaD $190 (male: CaD$ 176; female: CaD$ 207).[25] However, this Canadian study is not comparable with this current study given the socioeconomic and healthcare system

differences between the two countries. A more analogous study methodology and design for cost estimation was conducted in Australian sexual health clinics by Pirotta *et al*. This study showed that higher costs were associated with GW among women (A$ 386) as compared to men (A$ 251), similar to the trends found in the current study.[24]

Limitations

The selection of participating specialities and the physicians of each specialty are important study limitations, as their patients may not be representative of the entire population of patients who sought treatment. Participating specialists were selected in order to include patients with a diagnosis of GW in South Korea. A low rate of bias was expected to be associated with this factor. The expectation was that a low percentage of patients would be treated by other specialists than those included in the study. Participating physicians were selected, accounting for different regions, in order to include results of regional differences in GW prevalence. The fact that there was major participation of physicians working in the private sector, and not in public sector is another limitation of this study. Nevertheless, the Korean Healthcare System implements universal health insurance coverage; therefore, the National Health Insurance Program in South Korea is a compulsory social insurance covering the entire population. It may be assumed that treatment quality, physician practice costs, and reimbursements were similar in public and private clinics. Any bias associated with the profile of participating physicians in terms of private and public sector was expected to be minimal.

Contributorship Statement

TSL, SKT, PKS, KY, AK, ARG, SMG, WJ, NL, and MR conceived and designed the experiments for this manuscript.

NL, MR, SKT, PKS, AK performed the experiments for this manuscript.

NL, MR analyzed the data for this manuscript.

NL, MR contributed reagents/materials/analysis tools for this manuscript.

All authors contributed to the writing of this manuscript.

Competing Interests

- T.S. Lee has no conflicts to declare.
- K. Yee was a paid contractor for Merck and Co. at the time of the study, and was an employee of Cubist Pharmaceuticals December 2014 – July 2015, which was acquired by Merck and Co. in January 2015.
- A. Kulkarni, S. Kothari-Talwar, and P.K. Singhal are employees of Merck and Co.
- S.M. Garland received Grants to her institution from the Commonwealth Department of Health for HPV genoprevalance surveillance post vaccination, Merck and Co., and Glaxo Smith Kline to perform phase 3 clinical vaccine trials: Merck to evaluate HPV in RRP post vaccination programme; CSL for HPV in cervical cancer study, and VCA for a study on the effectiveness of a public health HPV vaccine study, and a study on the associations of early onset cancers. Received speaking fees from MSD and SPMSD for work performed in her personal time. Merck and Co. paid for travel & accommodation to present at HPV Advisory board meetings.
- A.R. Giuliano is a member of Merck & Co, Inc. advisory boards. Her institution has received grants and contracts to support HPV-related research.

- N. Lara and M. Roset are employees of IMS Health, Barcelona, Spain, which is a paid consultant to Merck and Co.
- W. Ju has no conflicts to declare.

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Data Sharing Statement:

The data collected is the property of Merck & Co. Inc., and can be accessed with permission from Merck & Co. Inc.

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Figure Legends

Figure 1. GW Prevalence in South Korea

DERM: dermatology; GW: genital warts; OBGYN: obstetrics/gynecology; PCP: primary care physician; URO: urology

Figure 2. Mean Percentage of Male and Female GW Patients using an In-Office Treatment or Procedure During Treatment for GW in South Korea

DERM: dermatology; GW: genital warts; OBGYN: obstetrics/gynecology; PCP: primary care physician; URO: urology

Figure 3. Mean Percentage of GW Patients Using Both In-office and At-home Topical Medication During the Treatment for GW in South Korea

DERM: dermatology; GW: genital warts; OBGYN: obstetrics/ gynecology; PCP: primary care physician; URO: urology; inj: injection

Figure 4. Median Costs Associated with GW Diagnosis and Treatment in Male and Female Patients

GW: genital warts; PCP: primary care physician; DERM: dermatology; URO: urology; OB/GYN: obstetrics/gynecology

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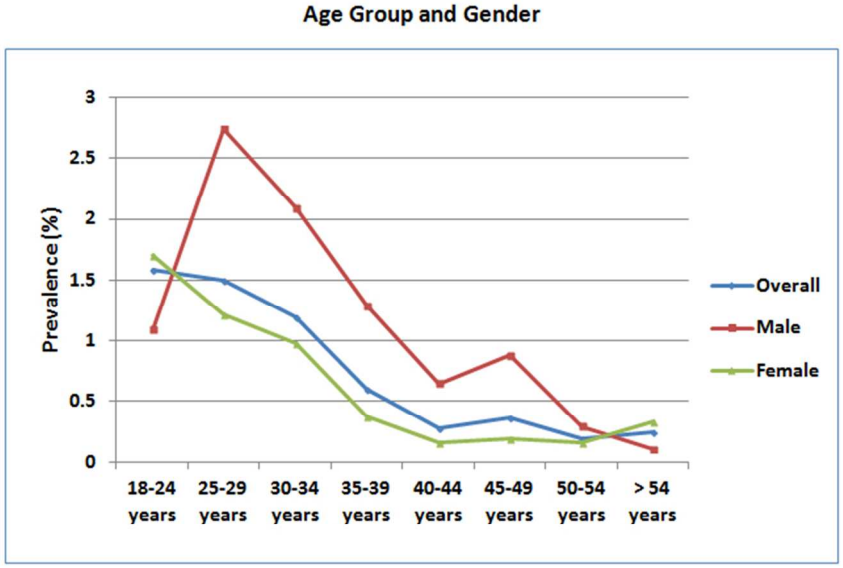

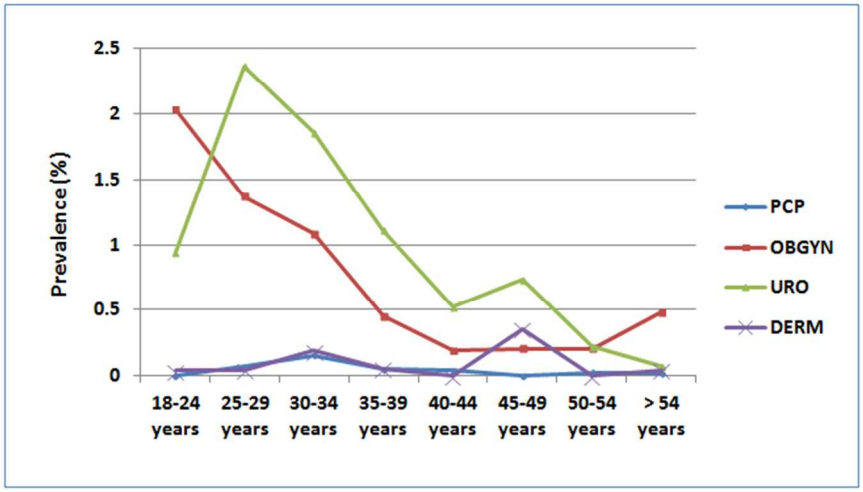

DERM: dermatology; GW: genital warts; OBGYN: obstetrics/gynecology; PCP: primary care physician; URO: urology

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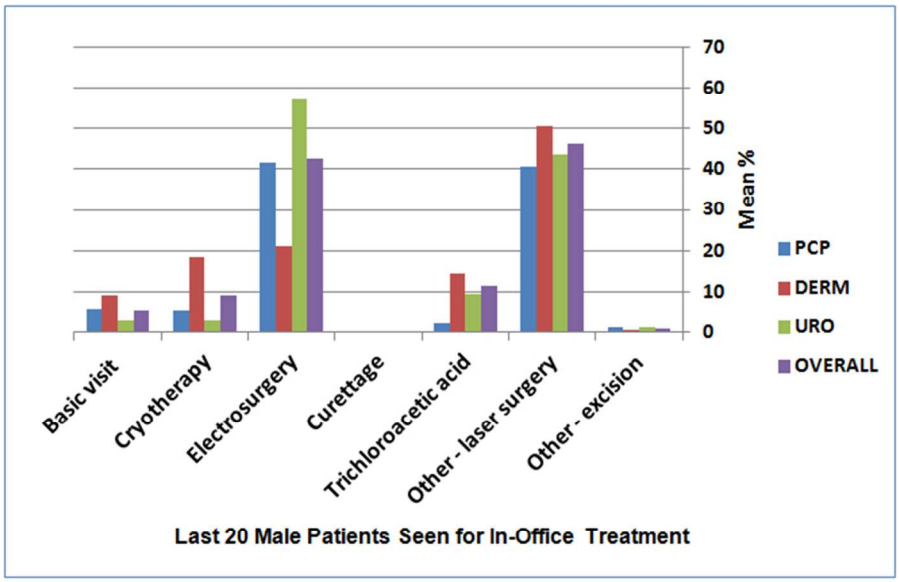

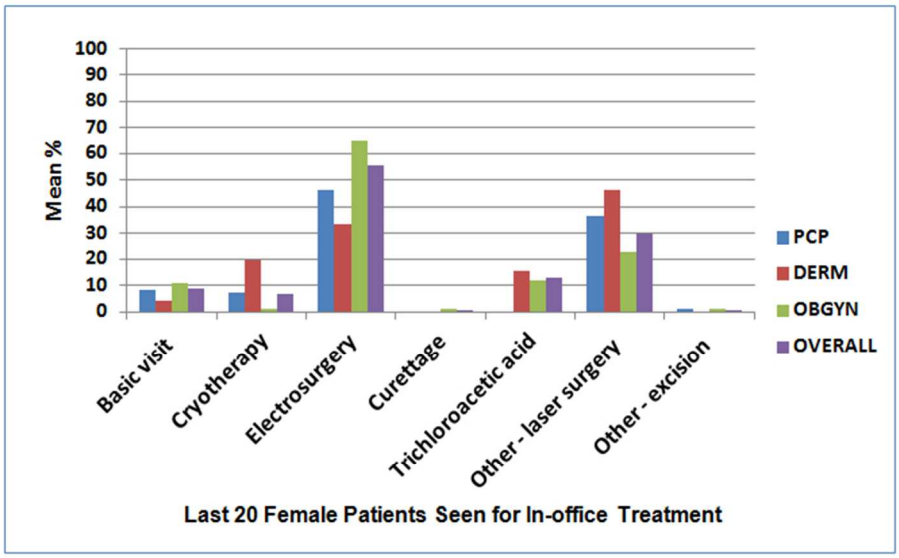

DERM: dermatology; GW: genital warts; OBGYN: obstetrics/gynecology; PCP: primary care physician; URO: urology

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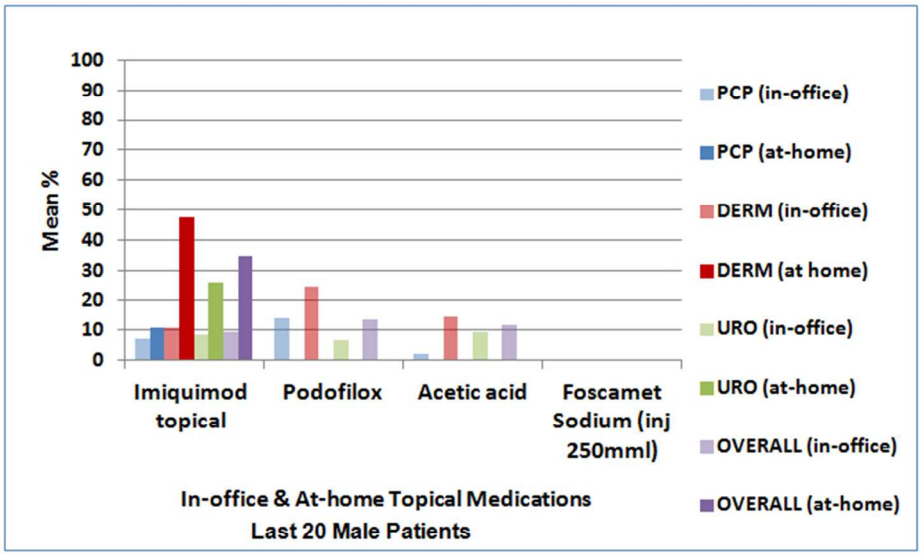

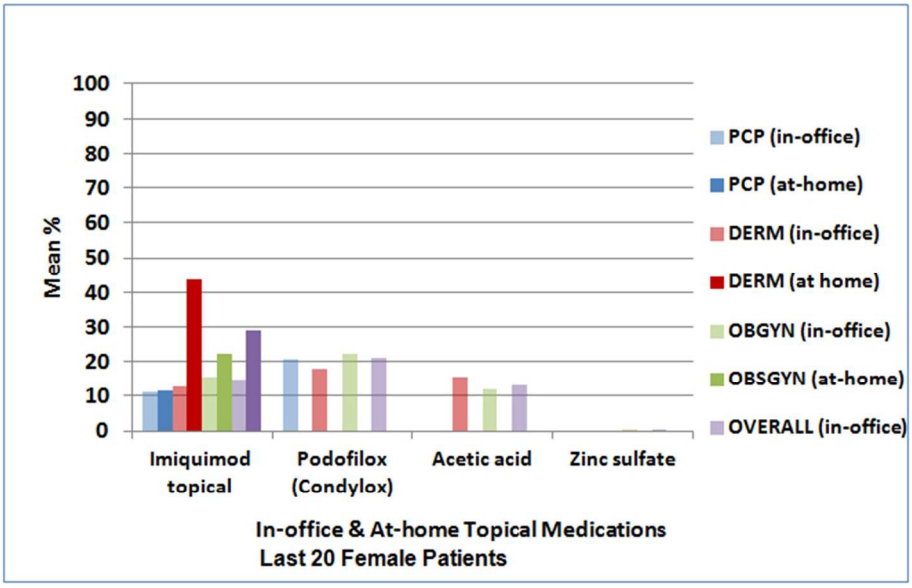

DERM: dermatology; GW: genital warts; OBGYN: obstetrics/ gynecology; PCP: primary care physician; URO: urology; inj: injection

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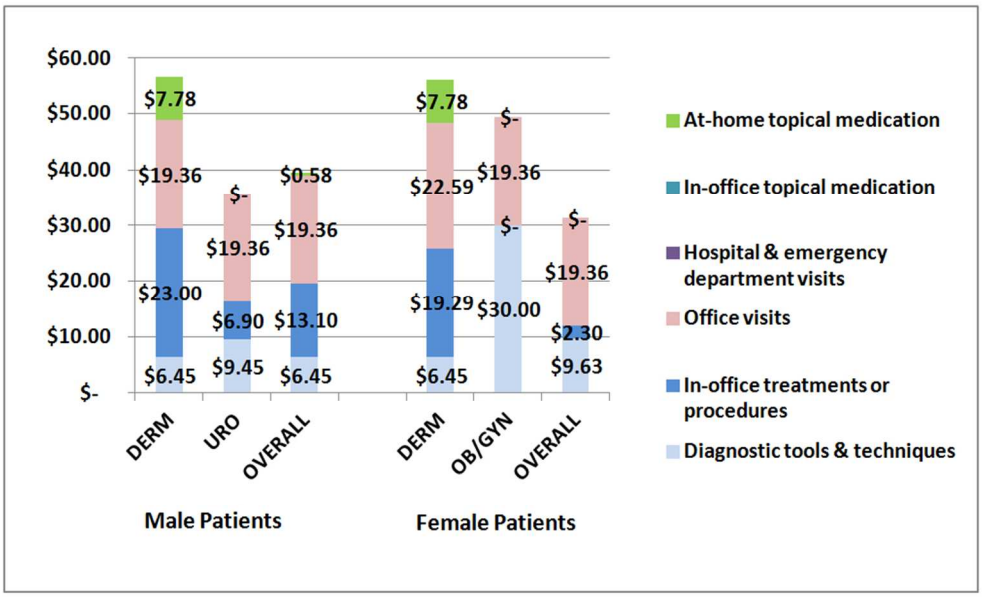

DERM: dermatology; GW: genital warts; OB/GYN: obstetrics/gynecology; PCP: primary care physician; URO: urology

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **–Pg. 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **– Pg. 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **–Pg. 4-5**
Objectives	3	State specific objectives, including any prespecified hypotheses – **Pg. 5**
Methods		
Study design	4	Present key elements of study design early in the paper – **Pg. 5-6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – **Pgs. 5-7**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up – **N/A** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls – **N/A** *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants –**Pgs. 5-7**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed – **N/A** *Case-control study*—For matched studies, give matching criteria and the number of controls per case – **N/A**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable – **Pgs. 6-8**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group – **Pgs. 6-8**
Bias	9	Describe any efforts to address potential sources of bias – **Pg. 3**
Study size	10	Explain how the study size was arrived at – **Pg. 6**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why – **Pg. 6-7**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding – **Pgs. 7-8**
		(*b*) Describe any methods used to examine subgroups and interactions – **Pg. 6-8**
		(*c*) Explain how missing data were addressed – **N/A**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **–N/A** *Case-control study*—If applicable, explain how matching of cases and controls was addressed **– N/A** *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy **Pgs. 6-8**
		(*e*) Describe any sensitivity analyses – **N/A**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed – **Pgs. 5-6, 9**
		(b) Give reasons for non-participation at each stage – **Pgs. 5-6**
		(c) Consider use of a flow diagram – **N/A**
Descriptive data	14*	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders – **Pgs. 5-6, and 9-11**
		(b) Indicate number of participants with missing data for each variable of interest –**N/A**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) – **N/A**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time –**N/A**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure –**N/A**
		Cross-sectional study—Report numbers of outcome events or summary measures – **Pgs. 11-14**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – **Pgs. 11, 16**
		(*b*) Report category boundaries when continuous variables were categorized – **N/A**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. – **N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses – **N/A**
Discussion		
Key results	18	Summarise key results with reference to study objectives – **Pgs. 14-17**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – **Pg. 17**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence – **Pgs. 14-17**
Generalisability	21	Discuss the generalisability (external validity) of the study results – **Pgs. 14-17**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based – **Pg. 19**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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A Cross Sectional Study Estimating the Burden of Illness Related to Genital Warts in South Korea

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Title: A Cross Sectional Study Estimating the Burden of Illness Related to Genital Warts in South Korea

Running Head: Cross Sectional Study: Estimating the Burden of Genital Warts in South Korea

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ABSTRACT

Objectives: Estimate the prevalence of genital warts (GW) and GW-related healthcare resource use and costs among male and female patients seeking treatment in South Korea.

Design: To estimate GW prevalence, physicians in 5 major South Korean regions recorded daily logs of patients (N=71,655) seeking care between July 26 and September 27, 2011. Overall prevalence estimates (and 95% CIs) were weighted by the estimated number of physicians in each specialty and the estimated proportion of total patients visiting each specialist type. Healthcare resource use was compared among different specialties. Corresponding p-values were calculated using Mann-Whitney U tests.

Setting: The database covers 5,098 clinics and hospitals for five major regions in South Korea: Seoul, Busan, Daegu, Kwangju, and Daejeon.

Participants: Primary care physicians (PCPs; general practice/family medicine), OB/GYNs, UROs, and dermatologists (DERMs) with 2-30 years' experience).

Results: The estimated overall GW prevalence was 0.7% (95% confidence interval [CI]: 0.7-0.8%). Among women, GW prevalence was 0.6% (95% CI: 0.6-0.7%); among men prevalence was 1.0% (95% CI: 0.9-1.0%), peaking among patients aged 18-24 years. Median costs for GW diagnosis and treatment for male patients were US $58.2 (South Korean Won [KRW] ₩ 66,857) and US $66.3 (KRW ₩ 76,113) for female patients.

Conclusions: The estimated overall GW prevalence in South Korea was 0.7% and was higher for male patients. The overall median costs associated with a GW episode were higher for female patients than for male patients.

Abstract word count: 232

Keywords: genital warts, healthcare resource use, South Korea

Strengths and limitations of this study

- Strength: This study is novel, due to the limited existing research on GW prevalence and cost in South Korea and the presence of data across multiple physician specialties and geographic regions.
- Limitations: Participating physicians having an increased likelihood to treat GW patients, possibly resulting in an overestimation of GW in South Korea.
- GW prevalence was not estimated from a random sample of physicians. National prevalence estimates were based on the physician population available from the IMS database, which may not have included all physicians in South Korea.
- GW patients who did not seek healthcare treatment for GW were not included.
- Potential bias may exist, related to the information source (physician survey) and the direction of bias is unknown.

BACKGROUND

Human papillomavirus (HPV) infections are the etiologic agents of genital warts (GW) and squamous intraepithelial lesions.[1] HPV is one of the most frequent sexually-transmitted viral infections[2-3] and has more than 130 identified virus types.[4] HPV 6 and 11 alone are estimated to cause approximately 90% of GW infections.[5] GW are highly infectious and nearly 65% of individuals with an infected partner develop lesions within 3 weeks-8 months from the first contact.[3,5] HPV prevalence varies by age and is higher among women and more common for young women with a new sexual partner.[6] Research suggests that an estimated 6.2 million new infections occur annually in individuals aged 14-44 years in the United States.

Data on national GW incidence by country are limited, and prevalence estimates by country range widely from 1.4% (Spain)[7] to 25.6% (Nigeria).[8, 9] In a recent systematic review undertaken to determine worldwide GW incidence and prevalence (from published data, January 2001-January 2012), GW incidence differed in regional distributions from 101-205, 118-170, and 204 new GW cases per 100,000 people in North America, Europe, and Asia, respectively. Age-specific GW incidence peaked for male patients aged 25-29 years and female patients 20-24 years, and remained significant in patients aged 30-45 years.[3]

Available GW treatments include patient-applied (home-based) chemicals (podofilox, imiquimod), provider-administered (office-based) chemicals (podophyllin, trichloracetic acid, interferon), and ablative treatment (cryotherapy, surgery, laser).[10] GW treatment and management can result in significant direct and indirect costs, and can cause a considerable financial burden, involving frequent physician office visits, medication application, and mechanical removal of warts. A study assessing incidence and economic burden on US commercially-insured patients reported estimated costs at $760 per 1,000 individuals in the

general population in 2004, with total costs exceeding $220 million.[11] Another study evaluating the economic burden of GW in Belgium, found similar conclusions related to overall costs. The estimated 7,989 annual number of diagnosed GW patients led to an estimated annual cost of €2.53 million.[12]

To date, there has been little research in South Korea to assess GW incidence and prevalence. A study conducted in South Korea among patients visiting urology (URO) and obstetrics/gynecology (OB/GYN) clinicians observed a GW prevalence of 0.4% with a higher prevalence among young patients. Among patients with GW, 21% reported to have suffered a GW recurrence.[13] As such, the burden of GW may have a larger economic impact on society than previously estimated. Given the lack of available data in South Korea, the current study was designed to estimate GW prevalence in physician practices, and GW-related healthcare resource use and costs in South Korea among male and female patients aged 20-60 years.

METHODS

Study Design

This was a cross-sectional study conducted via survey in the major regions of South Korea to estimate GW prevalence in physician practices, and GW-related healthcare resource use and costs in South Korea among male and female patients. In addition, patients diagnosed with GW were stratified as new, existing, recurrent, and resistant cases. The study protocol and list of participating institutions were submitted to the participant hospitals' Institutional Review Boards (IRBs). The study protocol was reviewed and approved by the National Evidence-based Health Care Collaborating Agency (NECA), the SMG-SNU University Medical Center, and the Ewha Women's University Mokdong Hospital ethics committees. No confidential patient-level data was collected for this study.

Inclusion and Exclusion Criteria

Participating Physicians

Participating physicians were identified through the Korean Intercontinental Marketing Services (KR IMS) database, which contains nationwide data published by the Health Insurance Review and Assessment (HIRA) Service. The database covers 5,098 clinics and hospitals for 5 targeted specialties in 5 major regions in South Korea: Seoul, Busan, Daegu, Kwangju, and Daejeon. Enrollment in the National Insurance System is mandatory for all clinics and hospitals, and are monitored by the HIRA in South Korea. Given the characteristics of the Korean healthcare system, which provides universal coverage, a specific inclusion quota by practice sector (private and public) was not defined. It is assumed that results of treatment pathways, quality, practice of physicians, resources, and costs should then be similar for public and private hospitals.

Physicians included in this study:

a) provided informed consent to participate and were specialists, including primary care physicians (PCPs); general practice/family medicine, OB/GYNs, UROs, and dermatologists (DERMs) with 2-30 years' experience);

b) devoted at least 30% of their time seeing and treating patients in outpatient visits, 3 or more work days per week (as opposed to inpatient surgeries, teaching, or other activities);

c) treated ≥75 patients in outpatient visits in a typical week; and

d) treated ≥50% of patients aged 20-60 years in outpatient visits.

Healthcare Costs and Resource Use

Referral patterns, resource use, and costs for GW patients were captured through a 30-minute face-to-face physician survey from July 26, 2011 to September 27, 2012. This survey was conducted after the physicians' daily logs. The survey included questions related to resource use as part of the usual course of diagnoses, treatment (treatments and procedures performed in-office and topical treatments applied in-office or prescribed at home), and follow-up care (medical visits, emergency room [ER] visits, hospitalizations) of typical GW patients in their practice. Survey questions were included to determine patient referral patterns in the practice, from PCPs to specialists and between specialists. Referral patterns were assessed from the physician survey, including the percentage of patients consulted directly by PCP, DERM, or URO, and the percentage of patients referred from another physician.

Costs were also reported by physician specialty in 2014 US dollars, converted from the South Korean Won (KRW). The costs per unit of healthcare service were collected from the HIRA Service, and unit cost was applied to the described health resources. For instance, if a particular treatment procedure cost approximately KRW ₩100 and on average, only 50% of patients actually received that treatment, then the cost for a typical patient would be KRW ₩50. Costs were summed across healthcare units to compute the total mean cost of GW for a typical patient.

Statistical Analysis

All study outcomes were summarized descriptively. P-values were calculated for comparison between the groups (ie, region, age, sex, and physician specialty) using t-tests or the Mann-Whitney U-test for continuous variables; Chi-square tests or Fisher Exact tests were used for binary or categorical variables.

GW prevalence of new or existing cases was calculated by physician specialty type, based on the number of new or existing cases observed, divided by the total number of patients who were seen during the 2-week study period. Using the national population (18-60 years) [14] and the prevalence of GW in South Korea, the age-adjusted estimate for the number of GW cases in South Korea was projected. Using the distribution of patients with new and existing GW in each age group, the expected number of cases of GW was estimated. The weighted prevalence was calculated based on the proportion of GW patients at the national level seen by each specialist type, multiplied by the total number of patients in the study, and divided by the total number of patients seen by each specific specialty. Prevalence was calculated using normal distribution, due to the large number of patients recorded in the daily logs. [15]

Prevalence estimates were stratified by age group, sex, and physician specialty. Number, mean, and 95% confidence intervals (CIs) were reported. Each physician specialty type reported the number and percentage of new or existing GW patients. Recurrent and resistant cases for existing GW patients were also reported.

RESULTS

Prevalence

A total of 200 physicians participated in the study (Table 1).

Table 1. Participating Physicians by Region and GW Cases by Specialty in South Korea[a]

Participating Physicians by Region in South Korea					
Region	PCP (n=50)	DERM (n=35)	OB/GYN (n=65)	URO (n=50)	Overall (n=200)
Busan	6 (12.0%)	5 (14.3%)	9 (13.8%)	9 (18.0%)	29 (14.5%)
Daegu	3 (6.0%)	3 (8.6%)	8 (12.3%)	7 (14.0%)	21 (10.5%)

Participating Physicians by Region in South Korea					
Region	**PCP (n=50)**	**DERM (n=35)**	**OB/GYN (n=65)**	**URO (n=50)**	**Overall (n=200)**
Daejeon	2 (4.0%)	2 (5.7%)	5 (7.7%)	4 (8.0%)	13 (6.5%)
Gwangju	2 (4.0%)	3 (8.6%)	4 (6.2%)	4 (8.0%)	13 (6.5%)
Seoul	37 (74.0%)	22 (62.9%)	39 (60.0%)	26 (52.0%)	124 (62.0%)
Total Physicians	50	35	65	50	200
GW Cases by Specialty in South Korea					
Patients with GW	7 (0.01%)	15 (0.1%)	147 (0.8%)	133 (0.8%)	302
New or existing GW					
New Case[b]	4 (57.1%)	6 (40.0%)	74 (50.3%)	78 (58.6%)	163 (53.6%)
Existing Case[c]	3 (42.9%)	9 (60.0%)	73 (49.7%)	55 (41.4%)	140 (46.3%)
Valid n Patients	7	15	147	133	302
Existing Cases					
Recurrent Case[d]	3 (100.0%)	3 (33.3%)	43 (58.9%)	29 (52.7%)	78 (55.7%)
Resistant Case[e]		6 (66.7%)	30 (41.1%)	26 (47.3%)	62 (44.3%)
Total Existing GW Patients	3	9	73	55	140

[a] Physician percentages were calculated over the corresponding valid n.

[b]New Case: GW not diagnosed previously by yourself or another physician.

[c] Existing Case: GW diagnosed previously by yourself or another physician.

[d]Recurrent Case: GW where previous episodes resolved with treatment.

[e]Resistant Case: GW where previous episodes were not resolved with treatment.

DERM: dermatology; GW: genital warts; OB/GYN: obstetrics/gynecology; PCP: primary care physician; URO: urology

Regional differences ($p<0.05$) ranged from a high prevalence of GW in Gwangju followed by Busan. The lowest prevalence was observed in Daejeon (Table 2).

Table 2. GW Prevalence among Male and Female Patients in South Korea by Region (Weighted Data)

Region	Average Number of All Patients[a] (n)	Patients Per Physician (n)	Patients with New or Existing GW (n)	Patients with New or Existing GW (%, 95% CI)[b]
Busan	11,214	387	60	1.0 (0.8; 1.1)
Daegu	6,773	322	26	0.6 (0.5; 0.8)
Daejeon	4,078	314	3	0.6 (0.4; 0.8)
Gwangju	5,030	387	44	1.5 (1.3; 1.7)
Seoul	44,560	359	169	0.7 (0.7; 0.8)
Overall	71,655	358	302	0.8 (0.8; 0.9)

[a]'All patients' includes all patients reported for the corresponding region.

[b]Percentage and 95% confidence intervals were calculated, accounting for the number of patients with identified genital wart status; weighted data.

CI: confidence interval; GW: genital warts

GW prevalence varied by age (Figure 1). There was a higher prevalence among men than among women. For men and women, GW prevalence generally decreased as age increased (Figure 1). URO and OB/GYN physicians reported a higher prevalence of GW patients. Few GW patients were treated by a PCP or DERM (Figure 2). The frequency of existing GW was slightly higher among patients treated by a DERM than in the remaining specialties. The

percentage of patients who were resistant to GW treatment differed in PCP consultations and DERM consultations (Table 1).

Referral Patterns, Healthcare Resource Use and Costs

Male Patients

Few patients treated by participating physicians were referred by other physicians. The mean number of reported visits was similar across physician specialties (Table 3).

Table 3. Number of Office Visits during a GW Episode and Number of Hospital and ER Visits for Male and Female Patients

	PCP (n=50)	DERM (n=35)	URO (n=50)	Overall (n=85)	p-value
Male Patients					
# Visits					
Mean (SD) (Range)	2.7 (1.3) (1.0-7.0)	3.3 (1.7) (1.0-8.0)	2.6 (1.20) (1.0-6.0)	2.9 (1.4) (1.0-8.0)	0.0355[b]
Valid n	28	33	49	82	
# Hospital or ER Visits					
Mean (SD) (Range)	0.8 (1.3) (0.0-4.0)	3.3 (2.1) (0.0-8.0)	0.4 (1.0) (0.0-5.0)	0.6 (1.5) (0.0-8.0)	0.1662[b]
Valid n	21	30	46	76	
	PCP (n=50)	**DERM (n=35)**	**OB/GYN (n=65)**	**Overall* (n=100)**	**p-value[b]**
Female Patients					
# Visits					
Mean (SD) (Range)	3.2 (1.7) (1.0-7.0)	4.0 (3.5) (1.0-20.0)	3.7 (1.7) (1.0-10.0)	3.8 (2.8) (1.0-20.0)	0.9966[b]
Valid n	18	28	65	93	
# Hospital or ER Visits					
Mean (SD) (Range)	0.6 (1.2) (0.0-4.0)	0.9 (1.8) (0.0-5.0)	0.4 (1.1) (0.0-5.0)	0.6 (1.4) (0.0-5.0)	0.1512[b]
Valid n	14	25	59	84	

[a]The overall column does not include Primary Care Physician records.

[b]Mann-Whitney U test (does not include Primary Care Physician records)

DERM: dermatology; ER: emergency room; GW: genital warts; OBGYN: obstetrics/gynecology; SD: standard deviation; URO: urology

The primary diagnostic technique was visual examination. URO used the HPV polymerase chain reaction (PCR) test in 12.7% of patients, biopsy in 7.3%, and urethoscopy/meatoscopy (depending on the anatomical site) in 3.0%. Based on the feedback from the last 20 male patients with GW, participating physicians reported the use of in-office treatments or procedures. Physicians used laser surgery in 46.4% of patients, followed by electrosurgery (42.5%), trichloroacetic acid (11.5%), and cryotherapy (9.0%). Cryotherapy was more frequently used by DERM (18.5%) than by PCP (5.4%) or URO (2.7%; $p<0.001$). Electrosurgery was more frequently used by URO (57.2%; $p<0.001$) compared to DERM and PCP. In-office topical medications were administered more often by DERM compared to other physicians, but the differences were not statistically significant (Figure 2).

Female Patients

The majority of female GW patients were not referred by another physician. The median number of visits reported was quite similar across physician specialties (Table 3). Participating physicians reported the mean in-office diagnostic tools and techniques, treatments or procedures based on the last 20 female GW patients who sought treatment. Diagnostic tools and techniques used most frequently by physicians to diagnose GW among female patients included visual examination (100% of patients), followed by Pap test (18.4%), biopsy (16%), histological examination (13%), HPV PCR test (11.3%), Hybrid Capture 2 HPV DNA test (8.2%), colposcopy (7.4%), and acetic acid tests (6.7%). There were differences in the use of particular diagnostic tools and techniques. OB/GYN used most of the tests more frequently than DERM, including the Pap smear (26.4%; $p<0.001$), colposcopy (9.9%; $p=0.0430$), histological examination (17.5%; $p=0.0100$), HPV PCR (16.2%; $p=0.0010$), and Hybrid Capture 2 HPV DNA Test (11.7%; $p=0.003$).

For female GW patients, electrosurgery was the most frequently used procedure by all physicians in the office (55.2%), followed by laser surgery (29.8%), trichloroacetic acid (13.0%), and cryotherapy (6.7%). Cryotherapy was administered more frequently by DERM (19.2% of patients) than by PCP (7.2%) or URO (1.2%; $p<0.001$); electrosurgery was performed more frequently by OB/GYN (64.5%) than by PCP, DERM, or URO.

During the course of treatment for a GW episode in female patients, 28.8% were prescribed imiquimod topical (Aldara) as an at-home topical medication (Figure 3). Foscamet sodium injection (250 mml, 500mml) was not reported as a treatment for female GW patients, and thus not shown for female patients in Figure 3. Imiquimod topical was used more frequently as an at-home medication compared to an in-office medication.

Healthcare Costs for Male and Female Patients

Figure 4 shows median costs associated with diagnosis and management of GW in male and female patients. Higher costs were associated with GW in female patients (median costs: US $66.3 (KRW ₩76,113) due to the significantly high costs for diagnosis, treatment procedures, and at-home medications administered by DERM or OB/GYN, compared to male patients whose median costs for GW were US $58.2 (KRW ₩66,857). In addition, statistically significant differences were observed between DERM and URO physicians for overall annual (p-values=0.0232), diagnostic tool and technique (p-values=0.0033), office visit (p-values=0.0355), and at-home topical medication prescription costs (p-values=0.0096). Among female patients, the overall annual cost comparison of DERM and OB/GYN practices presented no statistically significant differences (p-value=0.5919). However, significant differences by physician specialty for diagnostic tools and techniques (p-value<0.0001), in-office treatment and procedure costs (p-

values=0.0073), and topical medication prescription costs for at-home use (p-values=0.0037) were observed.

DISCUSSION

This cross-sectional study estimated the burden of GW in South Korea by estimating the prevalence of GW and GW-related resource use and costs among male and female patients aged 20-60 years. At the South Korean national level, the current study estimated GW prevalence at 1.0% for male, and 0.6% for female patients, which is lower compared to those reported in the United States, Denmark, Iceland, Norway, Sweden [16, 17] and in other studies conducted in South Korea.[18, 19] For instance, the US National Health and Nutrition Examination Survey (NHANES) found that from 1999 through 2004, 5.6% of survey respondents (aged 18-59 years) self-reported a GW diagnosis.[20] The percentage was higher among female patients 7.2% compared to male patients 4%.[2019] However, a previous study performed in Hong Kong that used a similar study design, estimated an overall GW prevalence rate of 0.9%, [21] which is similar to that observed in the current study, which ranged from 0.3-1.7% (Figure1).

An earlier Korean study of patients visiting URO and OB/GYN found that the predominant age for those diagnosed with GW was 25-29 years among male patients (prevalence: 1.8%) which is similar to that observed among the male population in our study. Also, in the earlier Korean study, the highest prevalence in the female population was among those aged 30-34 years (prevalence: 0.3%) [13], which differs from our study results: The highest prevalence of GW was found among female patients aged 18-24 years (1.2 %). A recent US study showed that HPV prevalence was found to be highest among women aged 20-24 years [22], as observed in this study.

Results from a systematic review of GW incidence and prevalence conducted in 4 Nordic European countries showed a wide range of prevalence in the self-reported history of GW. In surveys of general adult populations, 0.4% (Slovenia, sexually-active, aged 18-49 years) to 12.0% (Iceland, aged 18-45 years) of women reported a lifetime history of GW. [17~~16~~] The proportion of GW in male populations varied from 3.6% to 7.9% in Australia, Denmark, United Kingdom, and United States, and was 0.3% in Slovenia, from November 2004-June 2005. [21~~20~~] Also, results from a recent study of the Czech Republic population showed rising incidence of GW, with a 5.8% prevalence rate among patients aged 16-55 years. [23]

Differences in sexual behavior and use of different case-ascertainment methods for GW-related data may explain differences in prevalence found in these European studies compared to South Korea. In South Korea, the average age of a woman's first sexual intercourse experience is approximately 20 years, [24] compared to 16 years in the European studies. In the Kjaer, *et al*. study, [17~~16~~] GW prevalence was calculated using self-reported data, while in the current study only patients seeking healthcare were included. Therefore, the burden of GW results may have been higher due to those not seeking treatment or unreported cases.

In Australia, Pirotta, *et al*. estimated an annual incidence rate of 2.2 cases of GW per 1,000 Australians, with peak incidence in women aged 20-24 years, at 8.6 cases per 1,000, and in men aged 25–29 years, at 7.4 cases per 1,000.[25] In the United States, a study by Hoy, *et al*. found that GW incidence was highest among women aged 20-24 (4.6/1,000) and men aged 25-29 (2.7/1,000), in 2004.[11] Similarly, a study conducted in Canada found that overall GW prevalence between 1998 and 2006 was higher among men than women. Data from 2006 showed that prevalence was highest among women aged 20-24 years (3.9/1,000), whereas in men, the prevalence peaked at age 25-29 years (3.7/1,000).[26]

The most common treatment options for GW are podofilox, imiquimod, surgical excision, and cryotherapy.[27] In the current study, electrosurgery was the most frequently used therapy, followed by pharmacological topical treatments in the office and at home, and other surgical procedures.

In-office treatment for GW varied by physician specialty. Cryotherapy was more frequently administered by DERM than by other specialists, possibly because of expertise and access to equipment. Likewise, electrosurgery was more frequently used by URO and DERM than by PCP and OB/GYN. Imiquimod was the topical medication of choice for treatment of GW. As expected, patient referral to specialists was higher for PCP, who referred most men to URO and most women to OB/GYN. Specialists also referred patients to physicians within the same specialty (eg, DERM referred to another DERM, etc.).

GW diagnosis and treatment for male patients was associated with overall median costs of US $58.2 (KRW ₩66,857), and US $66.3 (KRW ₩76,113) for female patients. For male patients, the highest overall costs were due to office visits (49.0%), followed by in-office treatments and procedures (33.2%), and diagnostic tools and techniques (16.3%). For female patients, most costs were related to office visits (61.9%), followed by diagnostic tools and techniques (30.8%), and in-office topical medications (7.4%).

The United States, [28] Italy, [29] and Canada [26~~25~~] have conducted considerable research on GW-related healthcare costs. A Canadian claims data study found that the average cost per GW episode was CaD $190 (male: CaD$ 176; female: CaD$ 207).[26~~25~~] However, this Canadian study is not comparable with this current study given the socioeconomic and healthcare system differences between the two countries. A more analogous study methodology and design for cost estimation was conducted in Australian sexual health clinics by Pirotta et al.

This study showed that higher costs were associated with GW among women (A$ 386) as compared to men (A$ 251), similar to the trends found in the current study.[2524] Two hundred physicians and 71,655 GW patients were included in the study from five regions in South Korea. However, it is possible that the sample may not show a complete representation of the entire population of GW patients who sought treatment.

Limitations

The selection of participating specialities and the physicians of each specialty are important study limitations, as their patients may not be representative of the entire population of patients who sought treatment. Participating specialists were selected in order to include patients with a diagnosis of GW in South Korea. A low rate of bias was expected to be associated with this factor. The expectation was that a low percentage of patients would be treated by other specialists than those included in the study. Participating physicians were selected, accounting for different regions, in order to include results of regional differences in GW prevalence. The fact that there was major participation of physicians working in the private sector, and not in public sector is another limitation of this study. Nevertheless, the Korean Healthcare System implements universal health insurance coverage; therefore, the National Health Insurance Program in South Korea is a compulsory social insurance covering the entire population. It may be assumed that treatment quality, physician practice costs, and reimbursements were similar in public and private hospitals and clinics. Any bias associated with the profile of participating physicians in terms of private and public sector was expected to be minimal.

Contributorship Statement

TSL, SKT, PKS, KY, AK, ARG, SMG, WJ, NL, and MR conceived and designed the experiments for this manuscript.

NL, MR, SKT, PKS, AK performed the experiments for this manuscript.

NL, MR analyzed the data for this manuscript.

NL, MR contributed reagents/materials/analysis tools for this manuscript.

All authors contributed to the writing of this manuscript.

Competing Interests

- T.S. Lee has no conflicts to declare.
- K. Yee was a paid contractor for Merck and Co. at the time of the study, and was an employee of Cubist Pharmaceuticals December 2014 – July 2015, which was acquired by Merck and Co. in January 2015.
- A. Kulkarni, S. Kothari-Talwar, and P.K. Singhal are employees of Merck and Co.
- S.M. Garland received Grants to her institution from the Commonwealth Department of Health for HPV genoprevalance surveillance post vaccination, Merck and Co., and Glaxo Smith Kline to perform phase 3 clinical vaccine trials: Merck to evaluate HPV in RRP post vaccination programme; CSL for HPV in cervical cancer study, and VCA for a study on the effectiveness of a public health HPV vaccine study, and a study on the associations of early onset cancers. Received speaking fees from MSD and SPMSD for work performed in her personal time. Merck and Co. paid for travel & accommodation to present at HPV Advisory board meetings.

- A.R. Giuliano is a member of Merck & Co, Inc. advisory boards. Her institution has received grants and contracts to support HPV-related research.
- N. Lara and M. Roset are employees of IMS Health, Barcelona, Spain, which is a paid consultant to Merck and Co.
- W. Ju has no conflicts to declare.

Funding

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Data Sharing Statement:

The data collected is the property of Merck & Co. Inc., and can be accessed with permission from Merck & Co. Inc.

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Figure Legends

Figure 1. GW Prevalence in South Korea

GW: genital warts; PCP: primary care physician; OBGYN: obstetrics/gynecology; URO: urology; DERM: dermatology

Figure 2. Mean Percentage of Male and Female GW Patients using an In-Office Treatment or Procedure During Treatment for GW in South Korea

GW: genital warts; PCP: primary care physician; DERM: dermatology; OBGYN: obstetrics/gynecology; URO: urology

Figure 3. Mean Percentage of GW Patients Using Both In-office and At-home Topical Medication During the Treatment for GW in South Korea

GW: genital warts; PCP: primary care physician; DERM: dermatology; OBGYN: obstetrics/ gynecology; URO: urology; inj: injection

Figure 4. Median Costs Associated with GW Diagnosis and Treatment in Male and Female Patients

GW: genital warts; PCP: primary care physician; DERM: dermatology; URO: urology; OB/GYN: obstetrics/gynecology

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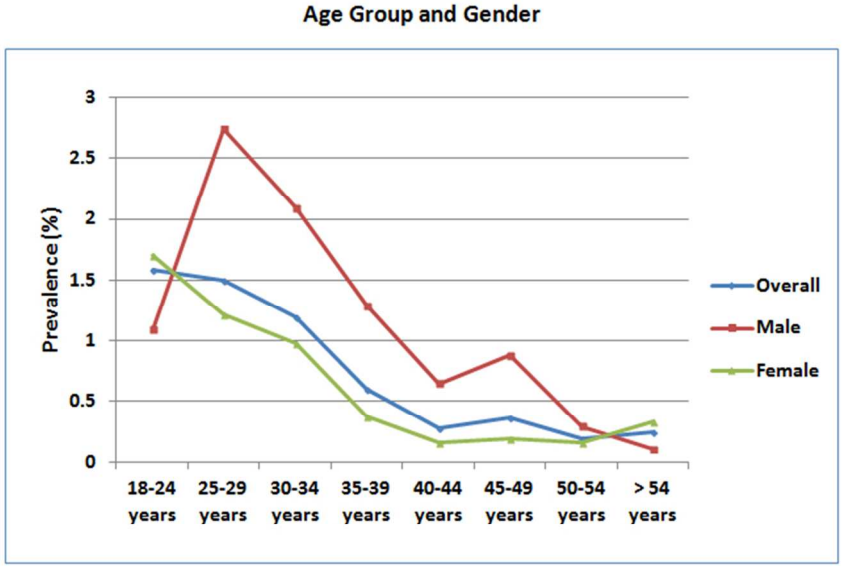

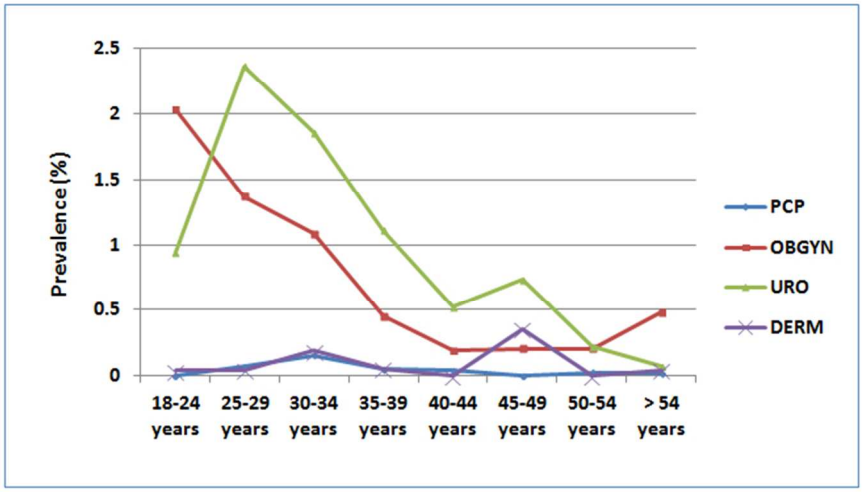

DERM: dermatology; GW: genital warts; OBGYN: obstetrics/gynecology; PCP: primary care physician; URO: urology

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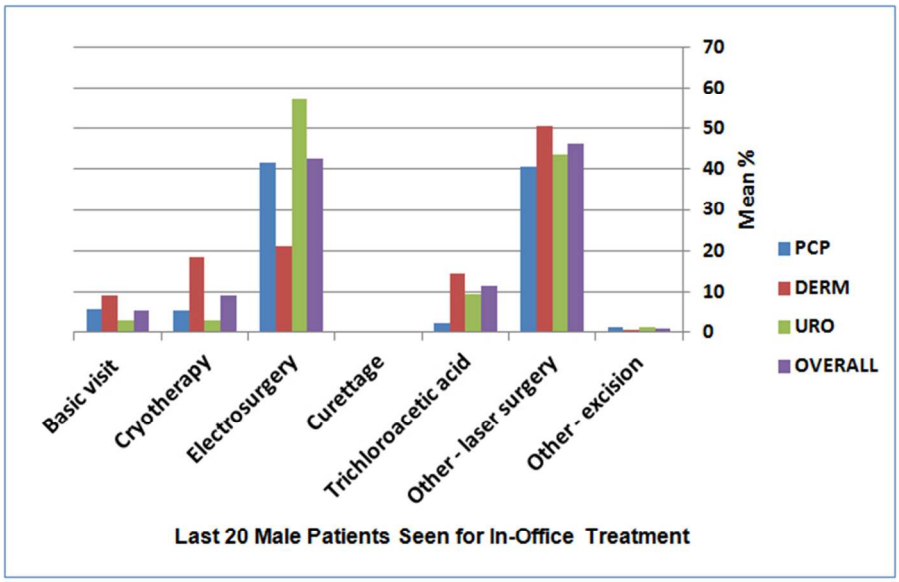

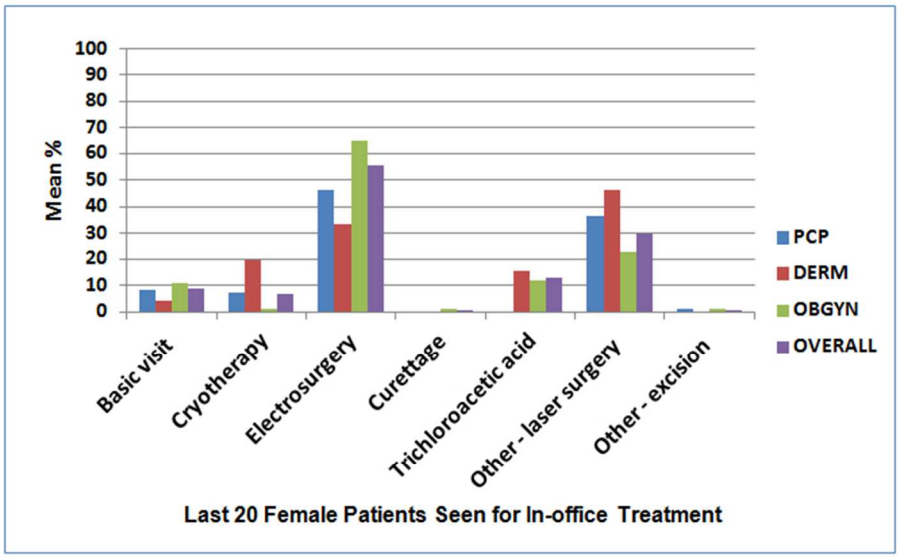

DERM: dermatology; GW: genital warts; OBGYN: obstetrics/gynecology; PCP: primary care physician; URO: urology

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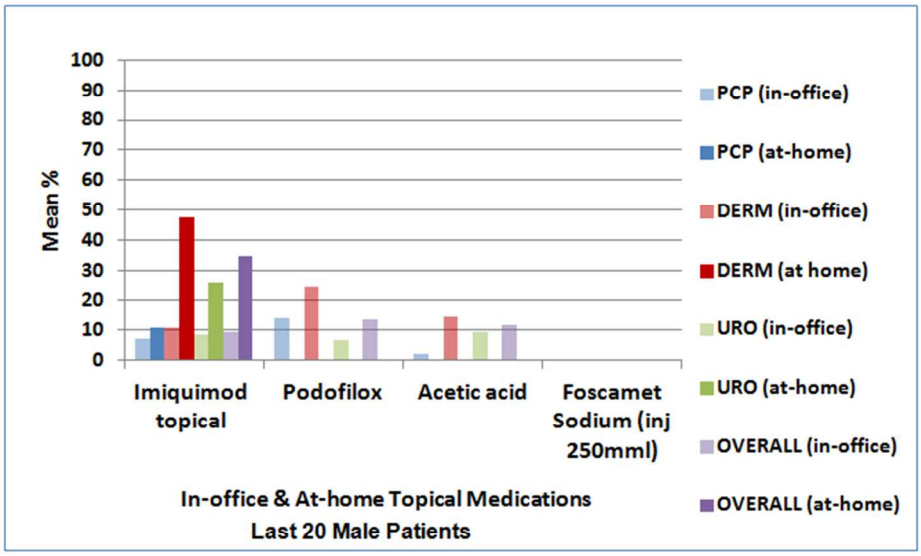

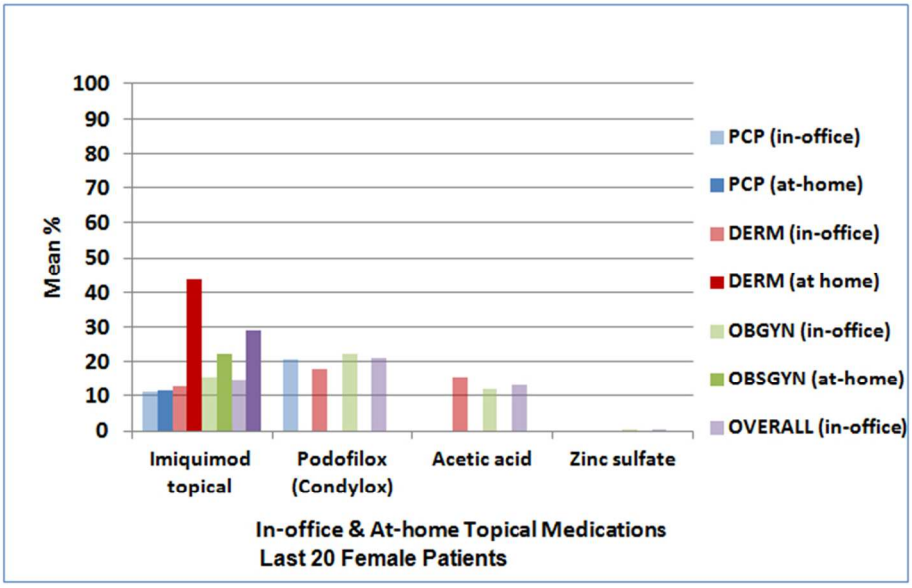

DERM: dermatology; GW: genital warts; OBGYN: obstetrics/ gynecology; PCP: primary care physician; URO: urology; inj: injection

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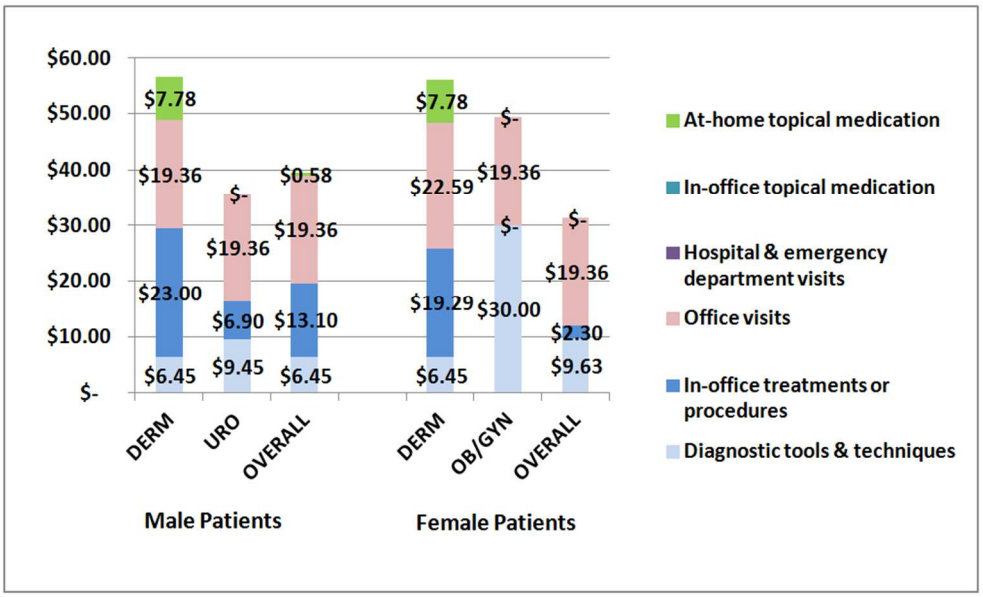

DERM: dermatology; GW: genital warts; OB/GYN: obstetrics/gynecology; PCP: primary care physician; URO: urology

87x54mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies
bmjopen-2016-014217

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **–Pg. 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **– Pg. 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **–Pg. 4-5**
Objectives	3	State specific objectives, including any prespecified hypotheses – **Pg. 5**
Methods		
Study design	4	Present key elements of study design early in the paper – **Pg. 5-6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – **Pgs. 5-7**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up – **Page 6** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls – **N/A** *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants –**Pgs. 5-7**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed – **N/A** *Case-control study*—For matched studies, give matching criteria and the number of controls per case – **N/A**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable – **Pgs. 3, 6-8**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group – **Pgs. 6-8**
Bias	9	Describe any efforts to address potential sources of bias – **Pg. 3; 14-17**
Study size	10	Explain how the study size was arrived at – **Pg. 6**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why – **Pg. 6-7**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding – **Pgs. 7-8**
		(*b*) Describe any methods used to examine subgroups and interactions – **Pg. 6-8**
		(*c*) Explain how missing data were addressed – **N/A**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **–N/A** *Case-control study*—If applicable, explain how matching of cases and controls was addressed **– N/A** *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy **Pgs. 6-8**
		(*e*) Describe any sensitivity analyses – **N/A**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed – **Pgs. 5-6, 9**
		(b) Give reasons for non-participation at each stage – **Pgs. 5-6**
		(c) Consider use of a flow diagram – **N/A**
Descriptive data	14*	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders – **Pgs. 5-6, and 9-11**
		(b) Indicate number of participants with missing data for each variable of interest –**N/A**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) – **N/A**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time –**N/A**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure –**N/A**
		Cross-sectional study—Report numbers of outcome events or summary measures – **Pgs. 11-14**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – **Pgs. 11-14**
		(*b*) Report category boundaries when continuous variables were categorized – **N/A**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. – **N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses – **N/A**
Discussion		
Key results	18	Summarise key results with reference to study objectives – **Pgs. 14-17**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – **Pg. 17**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence – **Pgs. 14-17**
Generalisability	21	Discuss the generalisability (external validity) of the study results – **Pg. 17**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based – **Pg. 19**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.