BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-025035
Article Type:	Research
Date Submitted by the Author:	26-Jun-2018
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Keywords:	gential warts, psychosocial impact, South Korea

A Cross-sectional Study Estimating the Psychosocial Impact of Genital Warts and Other Anogenital Diseases in South Korea

Short Title: GW: Psychosocial Impact in South Korea

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Keywords: Genital Warts, Psychosocial impact, South Korea

Acknowledgements: The authors acknowledge Furaha Kariburyo, MPH, of STATinMED Research, for medical writing assistance.

Abstract

Objectives: To estimate self-reported human papillomavirus (HPV) disease-related psychosocial impact among male and female patients in South Korea.

Design: In this multi-center cross-sectional study, psychosocial impacts were estimated using a one-time survey capturing HPV Impact Profile (HIP) results, *Cuestionario Específico para Condiloma Acuminado* (CECA; in Spanish) – 'Specific questionnaire for Condylomata Acuminata,' and the EuroQol-5 Dimension (EQ-5D) surveys. T-tests or Mann-Whitney U tests were used for continuous comparisons; chi-square or Fisher Exact tests were applied for categorical comparisons.

Setting: 5,098 clinics throughout Seoul, Busan, Daegu, Kwangju, and Daejeon (South Korea).

Participants: Patients with and without GW (males) and selected HPV diseases (females) visiting primary care physicians, obstetricians/gynecologists, urologists, and dermatologists with 2-30 years' experience.

Results: Of 150 male and 250 female patients, HIP scores showed 85.3% of male patients with genital warts (GW) and 32.0% without reported moderate psychological impact ($p<0.0001$). In categorized total scores, 88.5% of female patients with and 66.0% without selected HPV-related diseases reported moderate or high psychological impacts ($p=0.0004$). In the CECA questionnaire, male patients had mean (standard deviation) scores of 10.51 (3.79) in 'emotional health', and 15.90 (6.13) in 'sexual activity'. Female patients with GW reported lower scores in both dimensions with mean scores of 7.18 (4.17) in 'emotional health' and 10.97 (5.80) in 'sexual activity' ($p<0.0001$), indicating worse health-related quality of life (HRQOL). For the

EQ-5D, male patients with GW reported lower mean visual analog scale scores than those without (75.1 vs. 81.13, p<0.0135). Mean VAS score and utility values were lower for females with HPV-related diseases than those without (72.18 vs. 76.86 and 0.90 vs. 0.94, respectively).

Conclusion: In South Korea, GW in men and HPV-related diseases in women negatively impact patient well-being and HRQOL scores. Among women, those with GW suffered a greater psychosocial impact than those with other selected HPV-related diseases.

Keywords: genital warts, psychosocial impact, South Korea

Article Summary:

Strengths and limitations of this study

- Cross-sectional HIP, CECA, and EQ-5D surveys completed by patients were logged by multiple physician specialties and in different geographic regions in South Korea.
- Patients were stratified into male and female groups and further stratified by GW or HPV-related disease status (with/without)
- Patient survey results were used to assess psychosocial burden (general health, sexual activity, cervical cancer screening behavior, psychosocial impact, GW experience, socio-demographic information).
- Selection bias may have occurred due to the convenience sample approach used.

Introduction

Human papillomaviruses (HPVs) are common sexually transmitted viral infections in young people [1,2,3]. Of the 130 HPV types that have been identified and sequenced, approximately 40 have a predilection for the anogenital region. Although they are readily transmitted, and most are transient, they can cause disease that manifests as genital warts (GW) and squamous intraepithelial lesions on cervical Pap screenings, and high-risk types are the cause of anogenital cancers. HPV types 6 and 11 alone are estimated to cause most viral sexually transmitted infections [4,5]. GW can be exophytic, confluent, cauliflower-like tumors, and their typical morphologies can aid in diagnosis, although they can also be flat or atypical [6,7,8].

To date, few studies have focused on HPV prevalence and related disease among men and women residing in South Korea. The study, conducted among South Korean women, observed a low-risk HPV prevalence of 10.3% among those ages 20-29 years and 3.2% among women ages 50-59 years [9]. While another study observed an overall GW prevalence in South Korea of 0.7% [10].

Studies have shown that GW infection can have a tremendous psychosocial impact on patients [11, 12, 13]. Some of the highest rates of GW occur in adolescents and young adults at a time when individuals are particularly impacted by the stigma associated with a visible sexually transmitted infection (STI). Several key emotions have been identified in GW patients including anger, disgust, shame, embarrassment, depression, anxiety, worry and a feeling of being less desirable, which all can have an impact on sexual relationships [14]. In 1998, research by Maw *et al.* found that up to two-thirds of male and female GW patients made lifestyle changes that impacted their relationships [15].

Recognizing the profound impact that GW and other HPV-related diseases can have on patients has led to the creation of tools to assess the burden of these conditions, including the self-administered HPV Impact Profile (HIP) as developed and validated by Mast *et al.,* the European quality of life (EurQol)-5 dimension (EQ-5D), and the *Cuestionario Específico para Condiloma Acuminado* (CECA; in Spanish) – 'Specific questionnaire for Condylomata Acuminata'. These are standardized and commonly used instruments to measure health-related quality of life (HRQoL). [16,17,18]. The HIP was used in a study of Taiwanese women, and results showed that an abnormal Papanicolaou (Pap) result (including abnormal results and any grade of cervical cancer) has a significant psychosocial impact, and a greater impact for those diagnosed with GW [19]. Pirotta *et al.* also found a significant psychosocial impact on Australian women screened for and diagnosed with an HPV-related disease [20]. These women were found to be more likely to have their social lives disrupted, even more so than those being treated for high-grade cervical dysplasia [20].

Literature on the psychosocial impact of GW in South Korea is scarce. Most available research in the country focuses on cervical cancer, HPV knowledge and attitudes, or intention toward HPV vaccination [21,22,23]. The aim of this study was to evaluate the psychosocial burden of HPV-related diseases, including GW, in South Korea among male and female patients ages 20-60 years.

Materials and Methods

Study Design

A cross-sectional study was conducted from July 28, 2011 to November 30, 2011 in five major cities of South Korea: Seoul, Busan, Daegu, Kwangju, and Daejeon (Appendix Table A-1). The study targeted clinics where cervical cytology screenings, including GW screenings, were performed, and where men and women were seen for HPV-related diseases. The study was approved by the National Evidence-based Health Care Collaborating Agency (NECA), Borame University Hospital, the SMG-SNU University Medical Center, and the Ewha 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 an Intercontinental Marketing Services (IMS) database, a database of nationwide clinics published by Health Insurance Review and Assessment (HIRA). This database includes information pertaining to 5,098 clinics in the five targeted cities (Appendix Table A-2). All data collection for this study was conducted in the office or clinic of the participating physicians.

Patient and Public Involvement

Participant physicians invited their patients for study participation as part of routine practice by asking their patients if they were willing to participate in a one-time survey and giving them a

patient informed consent form with a short description of the survey. The physician provided verification on the survey regarding to which group the patient belonged (GW or control group) and administered the survey in the physician's office. Once the survey was completed, the patient's survey was placed in a sealed envelope and left at the physician's office to be sent or picked up by a research coordinator. Patients were not involved in the recruitment to and conduct of the study. Physicians were asked to read the corresponding questions to the patients to avoid any misinterpretation of questions. The results will not be disseminated to study participants. The current study was not a randomized controlled trial.

Female Patients

Female patients were included in the study if they were between the ages of 20 and 60 years, experienced an HPV-related event within the past 3 months, were in good self-reported health, and belonged to one of the following categories: a) Abnormal Pap test result with no definitive histology, conforming to the Bethesda Category-2001 category of squamous or glandular cell abnormality (for example: atypical cells of undetermined significance [ASCUS], atypical glandular cells of undetermined significance [AGUS], low-grade squamous intraepithelial lesion [LSIL] or high-grade squamous intraepithelial lesion [HSIL]) and no previous high-risk HPV test performed; b) receipt of positive high-risk HPV DNA test results after an abnormal Pap test, as defined in the previous category; c) diagnosis of external GW or treatment for recurrences;

d) histological diagnosis of HPV-related cervical dysplasia cervical lesion (eg, CIN1, CIN2, CIN 3); e) normal Pap result with no abnormal Pap test or definitive therapy within the past year; or f) two or more of the above conditions (not including GW patients) were categorized in the upper

level of disease. To enable categorizing of women into discreet disease groups of CIN versus GW, female patients were excluded from the study if they were diagnosed with GW and had any of the following: precancerous cervical lesions, abnormal Pap and HPV-positive, or abnormal Pap test results.

The control group was selected from the same clinic as the case group. Physicians provided verification on the survey regarding patient groups (GW or control group) and gave them the survey to complete in the physician's office. The physician sample was divided across primary care physicians (general practitioners and internal medicine), obstetrics/gynecologists, urologists, and dermatologists. The control group consisted of patients who have never had GW or received treatment for it or had surgery or therapy in the genital area and included all other patients from a physician's practice or clinic.

Male Patients

Male patients were included in the study if they were between ages 20 and 60 years, in good self-reported physical health, and belonged to one of the following categories: a) newly diagnosed or existing external GW within the past 3 months of study recruitment; and b) patients who had never been diagnosed with GW, prescribed GW treatment or had surgery or therapy in the genital area.

Male and female patients were excluded from the study if they: a) had presence of any other concurrent/active STI; b) were concurrently enrolled in clinical studies of investigational agents; c) had a history of known prior or recent (within 1 year of the enrollment date) HPV vaccination; d) had ongoing alcohol or drug abuse; e) were unable to give informed consent; or f)

had presence of any condition, which in the opinion of the investigator could interfere with the evaluation of the study objectives.

Survey Instruments

To measure the psychosocial burden (general health, sexual activity, cervical cancer screening behavior, psychosocial impact, GW experience, socio-demographic information), participants completed the three validated questionnaires; HIP (HPV Impact Profile), CECA (*Cuestionario Específico para Condiloma Acuminado* in Spanish– 'Specific questionnaire for Condylomata Acuminata') and EQ-5D (EuroQol-5 Dimension) surveys, which were translated to the Korean language and culturally pre-tested. Questionnaires were administered by the participating physician after patients were diagnosed with HPV-related disease. A pilot test was conducted using a small sample of physicians representing all four types of study physicians (two per specialty, eight total). This was to ensure that all survey questions and exercises were understood by respondents, and included culturally appropriate information.

HIP is a validated, 29-item self-administered questionnaire, designed to measure the psychosocial impact of HPV-related health conditions in women [15]. The response for each item ranges from 0 (lowest impact) to 10 points (highest impact). Items in the HIP survey were linearly transformed to a 0-100 scale, with higher scores indicating better health. To create scale scores, the mean was computed as the sum of the item scores over the number of items answered to account for missing data. If more than 50% of items on the scale were missing, the score was not computed. To create the total scale score, the mean was computed as the sum of all items over the number of items answered on all scales [24]. The scale uses visual-spatial, numeric, and verbal descriptive anchors to assess subject responses. This survey was adapted for use in male patients in consultation with the original developer and has undergone cognitive testing in the

United States. Overall HIP scores are categorized as: no or little impact (mean HIP score <40), moderate impact (between 40 and 70) and heavy psychological impact (mean HIP score >70) [19].

The CECA survey includes 10 questions across two domains: emotional and sexual activity [18,25]. CECA scores range from 0 (worst HRQoL) to 100 (best HRQoL). The EQ-5D survey is a two-part questionnaire, including descriptive and thermometer or visual analog scale (VAS), and serves as a generic validated instrument for use as a measure of HRQoL [26]. VAS scores range from 0 (death) to 100 (perfect health).

Statistical Analysis

All study outcomes were summarized descriptively. A descriptive analysis of the EQ-5D questionnaire was performed and numbers and percentages were provided. The Japanese version of the EQ-5D Instrument was used in this study to estimate the utilities associated with EQ-5D health status [27]. Japan was the first Asian country to develop its own preference EQ-5D weights in 2002. The model was chosen to represent Asian preference weights [28]. VAS scores and utility values were reported using the mean and standard deviation (SD) of the VAS score. VAS scores ranged from 0 (worst HRQoL) to 100 (best HRQoL), and utility values from 0 (death) to 1 (perfect health).

Scores obtained for male and female patients were compared according to GW diagnosis (in men) and HPV-related disease or GW diagnosis (in female patients). For continuous variables, comparisons were performed using the student t-test or Mann-Whitney U test. In addition, the effect size (mean difference between the two means divided by the *pooled* standard deviation) between groups has been calculated. For categorical variables, differences between

the groups were analyzed using the Chi-square or Fisher Exact test depending on patient distribution across response categories.

CECA scores were reported using the mean, SD, and 95% confidence interval (CI). Student t-tests were performed to compare CECA scores according to gender.

Results

Socio-demographic and Clinical Characteristics

A total of 400 patients participated in the study. Table 1 shows age, marital status, race, highest educational degree, and sexual activity according to gender and HPV diagnosis status. Approximately half of patients included in the study were age 30-44 years (45.3%), 85.9% were in a committed relationship, 51.6% were married, 2.3% earned an education lower than grade 12 (including vocational studies), 75.7% were employed, and 22.5% had no health insurance or other health care coverage.

Table 1. Socio-demographic Characteristics and Sexual Activity of Survey Participants in South Korea by Gender and GW Diagnosis (men) or HPV-related Diseases (women)

	Men (n=150)			Women (n=250)			
	With GW (n=75)	No GW (n=75)	P-value	HPV Disease (n=200)	No HPV Disease (n=50)	P-value	Overall
Age							
Mean	34.07	37.32	0.0422	34.90	35.56	0.6695	35.28
SD	9.48	9.96		9.63	10.32		9.77
Age group							
20-29 years	26 (34.7%)	19 (25.3%)	0.0194	70 (35.0%)	18 (36.0%)	0.9538	133 (33.3%)
30-44 years	40 (53.3%)	33 (44.0%)		86 (43.0%)	22 (44.0%)		181 (45.3%)
45-60 years	9 (12.0%)	23 (30.7%)		44 (22.0%)	10 (20.0%)		86 (21.5%)
Valid n	75	75		200	50		400
Committed relationship							
Yes	66 (88.0%)	62 (83.8%)	0.4596	170 (85.4%)	44 (88.0%)	0.6398	342 (85.9%)
No	9 (12.0%)	12 (16.2%)		29 (14.6%)	6 (12.0%)		56 (14.1%)
Valid n	75	74		199	50		398
Marital status							
Married	32 (42.7%)	45 (60.8%)	0.0976	98 (49.0%)	31 (62.0%)	0.4302	206 (51.6%)
Widowed/Divorced	1 (1.3%)	1 (1.4%)		9 (4.5%)	2 (4.0%)		13 (3.3%)
Separated	2 (2.7%)			6 (3.0%)	1 (2.0%)		9 (2.3%)
Never married	40 (53.3%)	28 (37.8%)		87 (43.5%)	16 (32.0%)		171 (42.9%)
Valid n	75	74		200	50		399
Highest degree							
Less than grade 12 including vocational education	1 (1.3%)	1 (1.3%)	0.1752	4 (2.0%)	3 (6.0%)	0.1159	9 (2.3%)
High school graduate/GED	18 (24.0%)	11 (14.7%)		67 (33.8%)	21 (42.0%)		117 (29.4%)
Some college/technical school including Associate's degree	12 (16.0%)	6 (8.0%)		54 (27.3%)	7 (14.0%)		79 (19.8%)
Baccalaureate degree	40 (53.3%)	48 (64.0%)		68 (34.3%)	16 (32.0%)		172 (43.2%)
Ever had Sexual intercourse							
Yes	75 (100.0%)	70 (93.3%)	0.0229	198 (99.0%)	46 (92.0%)	0.0038	389 (97.3%)
No		5 (6.7%)		2 (1.0%)	4 (8.0%)		11 (2.8%)
Valid n	75	75		200	50		400
Age at first sexual intercourse							
Mean	20.63	21.93	0.0470	21.92	22.84	0.1847	21.78
SD	3.95	3.79		4.19	4.18		4.11
Valid n patients	75	68		196	45		384

	Men (n=150)			Women (n=250)			
	With GW (n=75)	No GW (n=75)	P-value	HPV Disease (n=200)	No HPV Disease (n=50)	P-value	Overall
Number of sex partners in the last 5 years							
No partners		2 (2.9%)	0.0014	6 (3.0%)	2 (4.3%)	0.6072	10 (2.6%)
1 partner	9 (12.0%)	30 (42.9%)		103 (52.3%)	30 (65.2%)		172 (44.3%)
2-5 partners	47 (62.7%)	25 (35.7%)		65 (33.0%)	13 (28.3%)		150 (38.7%)
6-10 partners	10 (13.3%)	9 (12.9%)		9 (4.6%)			28 (7.2%)
11-15 partners	3 (4.0%)	1 (1.4%)		3 (1.5%)	1 (2.2%)		8 (2.1%)
16-20 partners	1 (1.3%)	2 (2.9%)		4 (2.0%)			7 (1.8%)
21-25 partners	3 (4.0%)			2 (1.0%)			5 (1.3%)
26-50 partners	1 (1.3%)			2 (1.0%)			3 (0.8%)
More than 50 partners	1 (1.3%)	1 (1.4%)		3 (1.5%)			5 (1.3%)
Valid n	75	70		197	46		388
Frequency of condom use							
Never	16 (21.3%)	26 (37.7%)	0.0614	86 (43.7%)	24 (52.2%)	0.2860	152 (39.3%)
Less than half the time	28 (37.3%)	13 (18.8%)		30 (15.2%)	10 (21.7%)		81 (20.9%)
About half the time	10 (13.3%)	12 (17.4%)		31 (15.7%)	3 (6.5%)		56 (14.5%)
Not always but more than half the time	16 (21.3%)	10 (14.5%)		26 (13.2%)	3 (6.5%)		55 (14.2%)
Always	5 (6.7%)	7 (10.1%)		15 (7.6%)	5 (10.9%)		32 (8.3%)
I have not had sexual intercourse in the last 12 months		1 (1.4%)		9 (4.6%)	1 (2.2%)		11 (2.8%)
Valid n	75	69		197	46		387
Sexual partners in lifetime							
Heterosexual partners	74 (100.0%)	70 (100.0%)		198 (100.0%)	46 (100.0%)		388 (100.0%)
Valid n	74	70		198	46		388
Sexual partners in the last 12 months							
Heterosexual partners	74 (100.0%)	69 (100.0%)		194 (100.0%)	46 (100.0%)		383 (100.0%)
Mean	2.57	1.80	0.0829	2.06	1.20	0.2046	2.01
SD	2.81	2.49		4.50	0.63		3.62
Valid n	74	69		194	46		383

GW=genital warts; HPV=human papillomavirus; SD=standard deviation; GED=general educational development

The sexual activity of surveyed patients according to gender and GW or selected HPV-related disease is shown in Table 1. Male GW patients reported a younger age at first intercourse compared to female patients (20.6 [4.0] vs. 21.9 [4.2]), and had a greater number of sexual partners (p=0.0014) than those without GW. A higher percentage of female patients with HPV-related diseases reported having had sexual intercourse compared to those without HPV-related diseases (99.0% vs. 92.0%, p=0.0038). No statistically significant differences were observed for any of the remaining sexual activity questions, as reported in Table 1.

Psychosocial Impact

HIP scores for male and female patients are summarized in Table 2. Significantly higher HIP scores were observed among men with GW compared to those without GW for all domains of the score except for 'control-life impact'. Eighty-five percent of men with GW and 32.0% of men without GW reported a moderate psychological impact (p<0.0001).

Table 2. HIP Questionnaire Scores of Participating Patients by GW and HPV-related Diagnosis in South Korea

	Men (n=150)				Women (n=250)*			
	With GW (n=75)	No GW (n=75)	ES	P-value	HPV Disease (n=200)	No HPV Disease (n=50)	ES	P-value
HIP total score								
Mean	50.90	36.13	1.69	<0.0001	53.37	44.98	0.68	<0.0001
95% CI	(48.8; 53.0)	(34.3; 38.0)			(51.8; 55.0)	(41.4; 48.6)		
Valid n	75	75			199	50		
Worries and concerns								
Mean	49.65	24.25	1.51	<0.0001	57.19	41.94	0.63	<0.0001
95% CI	(45.5; 53.8)	(20.8; 27.7)			(54.2; 60.2)	(35.5; 48.4)		
Valid n	75	75			199	49		
Emotional impact								
Mean	49.10	33.98	1.19	<0.0001	56.08	42.32	0.84	<0.0001
95% CI	(46.0; 52.2)	(31.3; 36.6)			(53.8; 58.4)	(37.8; 46.8)		
Valid n	75	75			199	50		
Sexual impact								
Mean	47.53	41.20	0.51	0.0019	50.81	49.80	0.07	0.6550
95% CI	(45.1; 50.0)	(38.1; 44.3)			(48.9; 52.8)	(45.3; 54.3)		
Valid n	75	75			197	49		
Self-Image								
Mean	49.00	41.63	0.76	<0.0001	47.66	45.17	0.19	0.2226
95% CI	(46.5; 51.5)	(39.8; 43.5)			(45.9; 49.5)	(41.4; 48.9)		
Valid n	75	75			199	50		

	Men (n=150)				Women (n=250)*			
	With GW (n=75)	No GW (n=75)	ES	P-value	HPV Disease (n=200)	No HPV Disease (n=50)	ES	P-value
Partner issues and transmission								
Mean	62.16	42.12	1.40	<0.0001	58.86	47.23	0.62	0.0001
95% CI	(59.1; 65.2)	(38.5; 45.8)			(56.2; 61.5)	(41.8; 52.6)		
Valid n	74	66			185	47		
Interactions with doctors								
Mean	51.31	33.28	0.90	<0.0001	46.75	45.73	0.20	0.6611
95% CI	(47.4; 55.3)	(25.2; 41.4)			(44.8; 48.7)	(40.8; 50.6)		
Valid n	71	30			199	50		
Control - life impact								
Mean	49.69	52.13	0.23	0.1643	48.48	52.37	0.31	0.0641
95% CI	(47.3; 52.0)	(49.6; 54.7)			(46.6; 50.4)	(49.2; 55.5)		
Valid n	75	75			199	50		
HIP total score categorized								
No or little impact	11 (14.7%)	51 (68.0%)		<0.0001	23 (11.5%)	17 (34.0%)		0.0004
Moderate impact	64 (85.3%)	24 (32.0%)			168 (84.0%)	30 (60.0%)		
Heavy psychological impact					9 (4.5%)	3 (6.0%)		
Valid n	75	75			200	50		

* HPV=human papillomavirus is included in this table. GW=genital warts; CI=confidence interval; HIP=human papillomavirus impact profile; ES=Effect size. Effect size (ES) >0.01 is considered significant.
HIP items range from 0 (lowest impact) to 10 point (highest impact).
CECA scores range from 0 (worst HRQL) to 100 (the best HRQL)
EQ-5D range from 0 (worst imaginable health state) to 100 (best imaginable health state)

When comparing women diagnosed with HPV-related disease to those without disease, significant differences were observed for the 'worries and concerns', 'emotional impact', and 'partner's issues and transmission' domains. In all domains, female patients with HPV-related disease had higher scores, reflecting a higher psychological impact (88.5% of female patients

with selected HPV-related diseases vs. 66.0% without reported a moderate or heavy psychological impact [p=0.0004]).

HIP scores by specific HPV-related disease were also conducted. In all domains except for 'control-life impact' and 'emotional impact', significant differences were identified. Higher scores, and thereby higher psychological impact, were reported by patients with external GW. All GW patients had either moderate or heavy psychological impact (90.0% and 10.0%, respectively). In all domains, female patients with selected HPV-related diseases had higher scores, reflecting a higher psychological impact (Appendix Table A-3).

CECA scores stratified by gender are shown in Figure 1. Women with GW reported significantly lower scores on the 'emotional health' (mean [SD], 7.2 [4.2]), and 'sexual activity' dimensions (11.0 [5.8]) compared to men with GW – 'emotional health' dimension (10.5 [3.8]) and 'sexual activity' dimension (15.9 [6.1]) – indicating worse HRQoL among women.

No significant differences were observed for problems reported by male patients in the EQ-5D descriptive system by GW diagnosis, as most male patients reported no problems. Among those who reported problems, the most frequent were 'pain-discomfort' (10.7%) and 'anxiety-depression' (12.7%, Table 3). Female patients with selected HPV-related diseases reported more problems related to the EQ-5D 'anxiety-depression' dimension than those without. Thirty-one percent of those with selected HPV-related diseases reported feeling moderately or extremely anxious or depressed, compared to 10.0% of female patients without HPV-related diseases. There were no statistically significant differences in the remaining EQ-5D items between female patients with and without HPV-related diseases (Table 3).

Table 3. EQ-5D Descriptive System Results by Male and Female patients with and without GW and Selected HPV-related Diseases in South Korea

	Men (n=150)			Women (n=250)		
	With GW (n=75)	No GW (n=75)	P-value	HPV Disease (n=200)	No HPV Disease (n=50)	P-value
Mobility						
I have no problems walking about	73 (97.3%)	75 (100.0%)	0.1545	193 (97.0%)	49 (98.0%)	0.6979
I have some problems walking about	2 (2.7%)			6 (3.0%)	1 (2.0%)	
Valid n	75	75		199	50	
Self-Care						
I have no problems with self-care	75 (100.0%)	75 (100.0%)	--	197 (99.0%)	50 (100.0%)	0.7762
I have some problems washing or dressing myself				1 (0.5%)		
I am unable to wash or dress myself				1 (0.5%)		
Valid n	75	75		199	50	
Usual Activities						
I have no problems with performing my usual activities	72 (96.0%)	75 (100.0%)	0.0802	196 (98.5%)	49 (98.0%)	0.8044
I have some problems with performing my usual activities	3 (4.0%)			3 (1.5%)	1 (2.0%)	
Valid n	75	75		199	50	
Pain - Discomfort						
I have no pain or discomfort	65 (86.7%)	69 (92.0%)	0.2900	165 (82.9%)	40 (80.0%)	0.6291
I have moderate pain or discomfort	10 (13.3%)	6 (8.0%)		34 (17.1%)	10 (20.0%)	
Valid n	75	75		199	50	
Anxiety - Depression						
I am not anxious or depressed	66 (88.0%)	65 (86.7%)	0.8061	136 (68.3%)	45 (90.0%)	0.0078
I am moderately anxious or depressed	9 (12.0%)	10 (13.3%)		56 (28.1%)	5 (10.0%)	
I am extremely anxious or depressed				7 (3.5%)		
Valid n	75	75		199	50	

EQ-5D=EuroQol-5 Dimension; GW=genital warts; HPV=human papillomavirus; SD=standard deviation

'HIP items range from 0 (lowest impact) to 10 point (highest impact).

CECA scores range from 0 (worst HRQL) to 100 (the best HRQL)

EQ-5D range from 0 (worst imaginable health state) to 100 (best imaginable health state)

EQ-5D descriptive system responses were also compared among female patients by HPV-related disease (Appendix Table A-4). The only two dimensions with significant differences were 'pain/discomfort' (p=0.0146) and 'anxiety/depression' (p=0.0387). A higher percentage of female GW patients reported being 'moderately anxious or depressed' and 'extremely anxious or depressed' (48.0%), followed by those with precancerous lesions (34.7%) and those presenting abnormal Pap test and HPV positive results (24.0%) (Appendix TableA- 4).

Table 4 shows VAS scores and utility values obtained from male participants according to GW diagnosis. Those patients with GW reported significantly lower mean VAS scores (75.3) than those without (81.1, p=0.0135). No significant differences in utility values according to GW diagnosis were identified.

Table 4 EQ-5D VAS Scores and Utility Values by Male Patients with and without GW and Female Patients with and without Selected HPV-related Disease in South Korea

	Men (n=150)					Women (n=250)				
	With GW (n=75)	No GW (n=75)	ES	P-value	Overall	HPV disease (n=200)	No HPV disease (n=50)	ES	P-value	Overall
VAS (EQ-5D)										
Mean	75.31	81.13	0.41	0.0135	78.16	72.18	76.86	0.30	0.0606	73.14
95% CI	(71.6; 79.0)	(78.4; 83.9)			(75.8; 80.5)	(69.9; 74.4)	(72.6; 81.1)			(71.2; 75.1)
Valid n	74	71			145	190	49			239
Utility values										
Mean	0.95	0.95	<0.01	0.7527	0.95	0.90	0.94	0.27	0.0773	0.91
95% CI	(0.9; 1.0)	(0.9;			(0.9; 1.0)	(0.9; 0.9)	(0.9; 1.0)			(0.9; 0.9)
Valid n	75	75			150	199	50			249

HPV = human papillomavirus; GW = genital warts; CI = confidence interval; EQ-5D = EuroQol-5 Dimension; ES = Effect size. Effect size (ES) >0.01 is considered significant.

'HIP items range from 0 (lowest impact) to 10 point (highest impact).
CECA scores range from 0 (worst HRQL) to 100 (the best HRQL)
EQ-5D range from 0 (worst imaginable health state) to 100 (best imaginable health state)

Female patients with selected HPV-related diseases showed numerically lower mean VAS scores (72.2) and utility values (0.90) than those without selected HPV-related diseases (76.86 and 0.94, respectively), but the differences were not significant. When comparing selected HPV-related diseases, the lowest VAS and utility scores (worst HRQoL) were observed in GW patients ($p<0.0001$, Appendix Table A-5).

Discussion

This cross-sectional study estimated the psychosocial burden of GW and HPV related diseases in South Korea by obtaining self-reported HPV disease-related information among male and female patients age 20-60 years presenting to clinics where cervical cytology screenings, including GW screenings, were performed, and where men and women were seen for HPV-related diseases. To our knowledge, this is the first study that has looked at the psychosocial burden of GW and HPV-related disease on patients' quality of life in South Korea. Higher HIP score values, reflecting a greater psychosocial impact of the disease, were recorded for men with GW than for those without GW (50.90 vs. 36.13) and in women diagnosed with HPV-related diseases than for those without (53.37 vs. 44.98).

Overall, female patients had a greater psychosocial impact compared to male patients (HIP scores: 51.69 vs. 43.51). Similarly, male patients had better HRQoL indicating lower psychosocial impact compared to female patients, as assessed by CECA scores (6.33 vs. 4.34).

VAS scores ranged from 0 (worst imaginable health status) to 100 (best imaginable health status), and female patients reported worse health status (73.14) compared to male patients (78.16), particularly female patients with HPV-related diseases (72.18). In addition, GW patients reported worse HRQoL scores compared to those without GW in the disease-specific HIP questionnaire. Furthermore, women reported poorer health status following a GW diagnosis than a CIN diagnosis. These results are consistent with a Chinese study by Wang *et al* [29] which reported that female GW patients had the highest mean HIP scores (52.2), showing a significant psychological impact, followed by patients with precancerous cervical lesions (48.6), HPV after abnormal Pap test results (45.8), abnormal Pap test results without HPV test (44.1), and HPV after abnormal Pap test results (43.1).

In the current study, HRQoL results suggest that GW in males and HPV-related disease (high-grade dysplasia requiring ablation treatment) in female patients had a negative impact on patient well-being and HRQoL scores. This study also observed that female GW patients suffered a major impact compared to those with other selected HPV-related diseases. Previous studies have shown that patients with GW had significantly lower quality of life, and substantial psychosocial burden with higher social stigma – especially when GW infection is symptomatic, visible to the naked eye, and found in the genital region [30,31,32]. In addition, a study that compared GW patients with asymptomatic genitourinary internal medicine patients observed that patients with GW had a significantly higher psychological burden because of the GW infection compared to the other patients. The study also observed that infection with GW not only influences the patient's physical wellbeing but also has a potentially detrimental effect on the patient's emotions [33].

This could explain the observed poorer health status in GW patients evaluated in this study.

Furthermore, the highest score was in the 'partner issue and transmission' category, followed by 'worries and concerns' and 'emotional impact', with a HIP mean score >60. The lowest scores were in the 'control-life impact' category (mean HIP score 45.20). A similar study using the HIP survey instrument in Australia found that the largest impact of GW on quality of life was in the domains of 'sexual impact', 'self-image,' and 'partner and transmission' [24].

Based on EQ-5D survey results, GW and selected HPV-related disease patients reported more problems related to 'anxiety-depression' than those without these conditions. The current study detected a lower impact of GW as assessed by EQ-5D than in the previous Canadian study [34]. HRQoL scores in each of the questionnaires reported by female study patients were descriptively compared among the study subgroups (abnormal Pap result, abnormal Pap and HPV positive results, precancerous lesions, and external GW). While GW has an impact on HRQoL in the current study, the precise impact is difficult to assess due to scarcity of data and the heterogeneity of the instruments used to compare scores of GW patients with those of the general population [35].

Shin *et al.* conducted a similar study in mainland China in 2012 and found that 56.4% of patients reported some problems in the 'anxiety and depression' dimension (highest), followed by 'pain and discomfort' (24.7%) and 'mobility' (3.5%) [16]. In a study from the United Kingdom in 2008, Woodhall *et al.* found that female GW patients had lower VAS and EQ-5D index scores than control patients, even after adjusting for age and gender. The difference was particularly notable in young women [36]. Consistent with the current study results, Woodhall *et al.* also reported that the 'pain and discomfort' and 'depression and anxiety' dimensions were the two most affected domains.

This study also observed that 60% of women with no GW reported a moderate impact in the HIP scoring. Reasons for this impact level among these patients were not evaluated. However, there is the possibility that these patients may have had other conditions during presentation at the clinic that may have impacted their HIP score.

Overall, the results of the current study suggest that a GW diagnosis has a great psychosocial impact on female patients. Other studies have provided evidence that the psychosocial impact of sexually transmitted disease diagnoses may be greater for women than for men. The origin of these differences is not clear, but they may be due to sexual infectivity and reproductive health [36]. Furthermore, research among women who received abnormal cervical smear test results have indicated that they often experienced psychosocial consequences including anxiety, fears about cancer, sexual difficulties, changes in body image and concerns regarding loss of reproductive function [13,37]. Shi *et al.* also indicated in their study that culture plays an important role, as conservative cultures (such as South Korea) view a diagnosis of a sexually transmitted disease such as GW as disgraceful. Consequently, patients would not seek support, even from their own families [16]. Additionally, continued study of HPV natural history among men from different geographic regions is necessary to elucidate the underlying HPV-related diseases occurring in these populations.

Limitations

The current study is limited, as selection bias may have occurred due to the convenience sample approach used. The data were collected in participating physician offices and clinics through questionnaires and interview-based surveys. Patients may have given expected rather than truthful answers, which may not give the true psychosocial impact. Moreover, only patients

who sought professional GW treatment were included in the study, which may not be generalizable to the entire South Korean GW population. As the study was cross-sectional in design, it can only report the impact of GW on the patients at the time the survey was taken, rather than longer-term impact. However, in a longitudinal study conducted to determine the impact of HPV status on quality of life (QoL) in oral cavity and oropharyngeal squamous cell carcinoma, results showed that QoL scores were lower in HPV positive patients. [38] The study design is a simple descriptive comparison of outcomes, so potential factors that might mediate or moderate the psychosocial effects of GW were not evaluated. We recommend that for future studies on GW in South Korea, multivariate analysis be carried out to address these factors.

Conclusion

The diagnosis of GW, a common sexually transmitted disease, has significant associated morbidity – largely due to the psychosocial impact GW have on patients. Prevention of all HPV-related diseases, cancers, and non-cancerous lesions is important. Vaccines that have broad protection against multiple HPV types should be considered. In addition, the results of this study can help direct guidelines for patient counseling and health education and emphasize the need to include HPV vaccine programs as a part of national vaccine programs. The purpose of this study was to determine the psychosocial impact of GW among male and female patients in South Korea utilizing various validated tools, given that literature related to the psychosocial impact of GW is scarce in this country. The current study results, utilizing HRQoL, suggest that GW in males and high-grade dysplasia requiring ablation treatment in female patients have a negative impact on patient well-being and HRQoL. The psychosocial burden was particularly greater among female GW patients compared to those with other selected HPV-related disease.

Although recent studies have looked at the psychosocial impact of GW on HRQoL in other places like China, [11] Singapore, [12] and the UK, [13] this study highlights the psychosocial impact of GW on HRQoL for infected patients in South Korea. Previously published studies used for comparison to the results of this study vary substantially in methodology and are different in nature due to the dissimilarities of GW across regions and cultures. However, the current study offers baseline data, and further research is encouraged to measure the psychosocial burden of GW in South Korea. Despite its limitations, the current study offers groundwork for measurement of the psychosocial impact of GW in South Korea that was previously unavailable.

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.

Funding

This study was funded by Merck and Co.

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.

Data Sharing Agreement

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

Supporting Information

Figure Legends

Figure 1. CECA Questionnaire Scores by Male and Female Patients with GW in South Korea

CECA=*Cuestionario Específico para Condiloma Acuminado* (in Spanish) – 'Specific questionnaire for Condylomata Acuminata'; GW=genital warts

Participating Physicians by Region in South Korea

DERM=dermatologist; OBGYN=obstetrician/gynecologist; PCP=primary care physician; URO=urologist

Table A-1. Target Number Of Clinics Within A Specialty Per City in South Korea

Table A-2. Participating Physicians by Region in South Korea

Table A-3. HIP Questionnaire Scores by Female Patients and selected HPV-related diseases in South Korea

HPV=human papillomavirus; HIP=HPV impact profile; Pap=Papanicolaou test; GW=genital warts; CI=confidence interval

Table A-4. EQ-5D Descriptive System Results by Female Patients and selected HPV-related Diseases in South Korea (excluding control group)

EQ-5D=EuroQol-5 Dimension; HPV=human papillomavirus; Pap=Papanicolaou test; GW=genital warts

Table A-5. EQ-5D VAS and Utility Scores for Female Patients by selected HPV-related Diseases in South Korea (excluding control group)

EQ-5D=EuroQol-5 Dimension; VAS=visual analog scores; HPV=human papillomavirus; Pap=Papanicolaou test; GW=genital warts; CI=confidence interval

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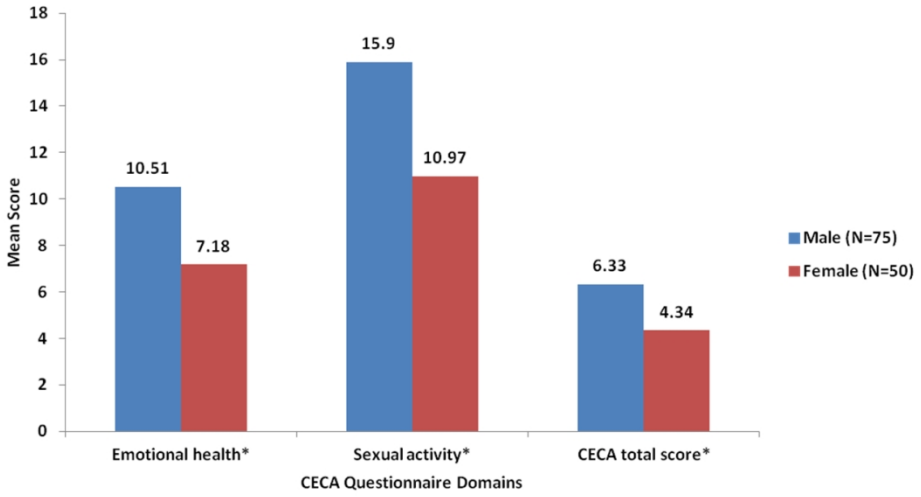

Figure 1. CECA Questionnaire Scores by Male and Female Patients with GW in South Korea / CECA=Cuestionario Específico para Condiloma Acuminado (in Spanish) – 'Specific questionnaire for Condylomata Acuminata'; GW=genital warts

364x193mm (96 x 96 DPI)

APPENDIX

Table A-1. Participating Physicians by Region in South Korea

	PCP (n=50)	DERM (n=35)	OB/GYN (n=65)	URO (n=50)	Overall (n=200)
Region					
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

DERM=dermatologist; OBGYN=obstetrician/gynecologist; PCP=primary care physician; URO=urologist

Table A-2. Target Number Of Clinics Within A Specialty Per City in South Korea

City	OB/GYN	URO	DERM	PCP	Overall	
	N	N	N	N	N	%
Seoul	37	24	20	31	112	60%
Busan	9	8	4	8	29	15%
Daegu	7	7	3	4	21	11%
Kwangju	4	4	2	3	13	7%
Daejeon	4	4	1	4	13	7%
Total	61	47	30	50	188	100%

Table A-3. HIP Questionnaire Scores by Female Patients and selected HPV-related diseases in South Korea

	HPV Disease (n=200)					
	Abnormal Pap (n=50)	Abnormal Pap and HPV positive (n=50)	Precancerous Lesions (n=50)	External GW (n=50)	No HPV Disease (n=50)	Overall
HPV Impact Profile total						
Mean	50.54	52.59	50.69	59.61	44.98	51.69
95% CI	(47.0;	(49.4;	(47.6; 53.8)	(57.2;	(41.4;	(50.2; 53.2)
Valid n	50	50	49	50	50	249
HPV Impact Profile total						
No or little impact	9 (18.0%)	7 (14.0%)	7 (14.0%)		17	40 (16.0%)
Moderate impact	40 (80.0%)	41 (82.0%)	42 (84.0%)	45 (90.0%)	30	198
Heavy psychological	1 (2.0%)	2 (4.0%)	1 (2.0%)	5 (10.0%)	3 (6.0%)	12 (4.8%)
Valid n	50	50	50	50	50	250
Worries and concerns						
Mean	52.64	54.20	54.73	67.14	41.94	54.18
95% CI	(46.0;	(48.2;	(49.3; 60.1)	(61.8;	(35.5;	(51.4; 57.0)
Valid n	50	50	49	50	49	248
Emotional impact						
Mean	53.16	56.24	54.37	60.52	42.32	53.32
95% CI	(48.8;	(51.2;	(49.6; 59.2)	(56.3;	(37.8;	(51.2; 55.5)
Valid n	50	50	49	50	50	249
Sexual impact						
Mean	49.30	48.85	51.73	53.30	49.80	50.61
95% CI	(45.7;	(45.6;	(46.6; 56.9)	(49.8;	(45.3;	(48.8; 52.4)
Valid n	50	48	49	50	49	246
Self-Image						
Mean	46.85	49.25	40.20	54.20	45.17	47.16
95% CI	(43.1;	(45.9;	(36.8; 43.6)	(51.2;	(41.4;	(45.5; 48.8)
Valid n	50	50	49	50	50	249
Partner issues and transmission						
Mean	55.42	57.73	51.71	70.07	47.23	56.51
95% CI	(50.0;	(52.5;	(45.8; 57.6)	(66.4;	(41.8;	(54.1; 59.0)
Valid n	48	47	43	47	47	232
Interactions with doctors						
Mean	42.47	47.33	46.26	50.93	45.73	46.55
95% CI	(38.7;	(43.5;	(42.4; 50.1)	(46.8;	(40.8;	(44.7; 48.4)
Valid n	50	50	49	50	50	249
Control - life impact						
Mean	49.33	49.73	49.66	45.20	52.37	49.26
95% CI	(45.5;	(46.3;	(45.9; 53.4)	(40.7;	(49.2;	(47.6; 50.9)

	HPV Disease (n=200)					
	Abnormal Pap (n=50)	**Abnormal Pap and HPV positive (n=50)**	**Precancerous Lesions (n=50)**	**External GW (n=50)**	**No HPV Disease (n=50)**	**Overall**
Valid n	50	50	49	50	50	249

HPV=human papillomavirus; HIP=HPV impact profile; Pap=Papanicolaou test; GW=genital warts; CI=confidence interval

Table A-4. EQ-5D Descriptive System Results by Female Patients and selected HPV-related Diseases in South Korea (excluding control group)

	Abnormal Pap Result (n=50)	Abnormal Pap Result and HPV positive (n=50)	Precancerous Lesions (n=50)	External GW (n=50)	Overall	P-value
Mobility						
I have no problems walking about	49 (98.0%)	50 (100.0%)	47 (95.9%)	47 (94.0%)	193 (97.0%)	0.3403
I have some problems walking about	1 (2.0%)		2 (4.1%)	3 (6.0%)	6 (3.0%)	
Valid n	50	50	49	50	199	
Self-Care						
I have no problems with self-care	50 (100.0%)	50 (100.0%)	48 (98.0%)	49 (98.0%)	197 (99.0%)	0.6193
I have some problems washing or dressing myself				1 (2.0%)	1 (0.5%)	
I am unable to wash or dress myself			1 (2.0%)		1 (0.5%)	
Valid n	50	50	49	50	199	
Usual Activities						
I have no problems with performing my usual activities	50 (100.0%)	50 (100.0%)	47 (95.9%)	49 (98.0%)	196 (98.5%)	0.1960
I have some problems with performing my usual activities			2 (4.1%)	1 (2.0%)	3 (1.5%)	
Valid n	50	50	49	50	199	
Pain - Discomfort						
I have no pain or discomfort	46 (92.0%)	43 (86.0%)	42 (85.7%)	34 (68.0%)	165 (82.9%)	0.0146
I have moderate pain or discomfort	4 (8.0%)	7 (14.0%)	7 (14.3%)	16 (32.0%)	34 (17.1%)	
Valid n	50	50	49	50	199	
Anxiety - Depression						
I am not anxious or depressed	40 (80.0%)	38 (76.0%)	32 (65.3%)	26 (52.0%)	136 (68.3%)	0.0387
I am moderately anxious or depressed	10 (20.0%)	10 (20.0%)	15 (30.6%)	21 (42.0%)	56 (28.1%)	
I am extremely anxious or depressed		2 (4.0%)	2 (4.1%)	3 (6.0%)	7 (3.5%)	
Valid n	50	50	49	50	199	

EQ-5D=EuroQol-5 Dimension; HPV=human papillomavirus; Pap=Papanicolaou test; GW=genital warts

Table A-5. EQ-5D VAS and Utility Scores for Female Patients by selected HPV-related Diseases in South Korea (excluding control group)

	Abnormal Pap (n=50)	Abnormal Pap and HPV positive (n=50)	Precancerous Lesions (n=50)	External GW (n=50)	Overall	p-value
VAS (EQ-5D)						
Mean	74.51	73.78	71.50	68.92	72.18	<0.0001
95% CI	(69.8; 79.2)	(70.0; 77.6)	(66.5; 76.5)	(64.2; 73.6)	(69.9; 74.4)	
Valid n	49	49	42	50	190	
Utility values						
Mean	0.94	0.93	0.89	0.85	0.90	<0.0001
95% CI	(0.9; 1.0)	(0.9; 1.0)	(0.9; 0.9)	(0.8; 0.9)	(0.9; 0.9)	
Valid n	50	50	49	50	199	

EQ-5D=EuroQol-5 Dimension; VAS=visual analog scores; HPV=human papillomavirus; Pap=Papanicolaou test; GW=genital warts; CI=confidence interval

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. 3**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **– Pg. 3**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **–Pg. 5-6**
Objectives	3	State specific objectives, including any prespecified hypotheses – **Pg. 6**
Methods		
Study design	4	Present key elements of study design early in the paper – **Pg. 7-11**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – **Pgs. 7-11**
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. 7-11**
		(*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. 10-11**
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. 10-11**
Bias	9	Describe any efforts to address potential sources of bias – **Pg. 22**
Study size	10	Explain how the study size was arrived at – **Pg. 7-11**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why – **Pg. 9-11**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding – **Pgs. 10-11**
		(*b*) Describe any methods used to examine subgroups and interactions – **Pg. 8-10**
		(*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. 7-11**
		(*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. 11 - 12**
		(b) Give reasons for non-participation at each stage – **Pgs. 7-9**
		(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. 7-9, 11-13**
		(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. 15-20**
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 – **N/A**
		(*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. 11-20**
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. 22-23**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence – **Pgs. 20-22**
Generalisability	21	Discuss the generalisability (external validity) of the study results – **Pgs. 20-22**
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. 1**

*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 Psychosocial Impact of Genital Warts and Other Anogenital Diseases in South Korea

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-025035.R1
Article Type:	Research
Date Submitted by the Author:	04-Dec-2018
Complete List of Authors:	Lee , Taek Sang ; SMG-SNU Boramae Medical Center, Department of Obstetrics and Gynecology Kothari-Talwar , Smita ; Merck and Co Inc Singhal, Puneet ; Merck and Co Inc Yee, Karen ; Cubist Pharmaceuticals Inc, Kulkarni , Amit ; Merck and Co Inc, Lara, Nuria; IMS Health Barcelona Roset , Montserrat ; IMS Health Economics and Outcomes Research, Giuliano, Anna; Lee Moffitt Cancer Center and Research Institute Garland, Suzanne; The Royal Women's Hospital, Microbiology and Infectious Diseases Department Ju, Woong; Ewha Womans University, School of Medicine
Primary Subject Heading:	Sexual health
Secondary Subject Heading:	Dermatology, Sexual health, Urology, Epidemiology
Keywords:	gential warts, psychosocial impact, South Korea

A Cross-sectional Study Estimating the Psychosocial Impact of Genital Warts and Other Anogenital Diseases in South Korea

Short Title: GW: Psychosocial Impact in South Korea

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Acknowledgements: The authors acknowledge Furaha Kariburyo, MPH, of STATinMED Research, for medical writing assistance.

Abstract

Objectives: To estimate self-reported human papillomavirus (HPV) disease-related psychosocial impact among male and female patients in South Korea.

Design: In this multi-center cross-sectional study, psychosocial impacts were estimated using a one-time survey capturing HPV Impact Profile (HIP) results, *Cuestionario Específico para Condiloma Acuminado* (CECA; in Spanish) – 'Specific questionnaire for Condylomata Acuminata,' and the EuroQol-5 Dimension (EQ-5D) surveys. T-tests or Mann-Whitney U tests were used for continuous comparisons; chi-square or Fisher Exact tests were applied for categorical comparisons.

Setting: 5,098 clinics throughout Seoul, Busan, Daegu, Kwangju, and Daejeon (South Korea).

Participants: Patients with and without GW (males) and selected HPV diseases (females) visiting primary care physicians, obstetricians/gynecologists, urologists, and dermatologists with 2-30 years' experience.

Results: Of 150 male and 250 female patients, HIP scores showed 85.3% of male patients with genital warts (GW) and 32.0% without reported moderate psychological impact ($p<0.0001$). In categorized total scores, 88.5% of female patients with and 66.0% without selected HPV-related diseases reported moderate or high psychological impacts ($p=0.0004$). In the CECA questionnaire, male patients had mean (standard deviation) scores of 10.51 (3.79) in 'emotional health', and 15.90 (6.13) in 'sexual activity'. Female patients with GW reported lower scores in both dimensions with mean scores of 7.18 (4.17) in 'emotional health' and 10.97 (5.80) in 'sexual activity' ($p<0.0001$), indicating worse health-related quality of life (HRQOL). For the EQ-5D, male

patients with GW reported lower mean visual analog scale scores than those without (75.1 vs. 81.13, p<0.0135). Mean VAS score and utility values were lower for females with HPV-related diseases than those without (72.18 vs. 76.86 and 0.90 vs. 0.94, respectively).

Conclusion: In South Korea, GW in men and HPV-related diseases in women negatively impact patient well-being and HRQOL scores. Among women, those with GW suffered a greater psychosocial impact than those with other selected HPV-related diseases.

Keywords: genital warts, psychosocial impact, South Korea

Article Summary:

Strengths and limitations of this study

- Cross-sectional HIP, CECA, and EQ-5D surveys completed by patients were logged by multiple physician specialties and in different geographic regions in South Korea.
- Patients were stratified into male and female groups and further stratified by GW or HPV-related disease status (with/without)
- Patient survey results were used to assess psychosocial burden (general health, sexual activity, cervical cancer screening behavior, psychosocial impact, GW experience, socio-demographic information).
- Selection bias may have occurred due to the convenience sample approach used.

Introduction

Human papillomaviruses (HPVs) are common sexually transmitted viral infections in young people [1,2,3]. Of the 130 HPV types that have been identified and sequenced, approximately 40 have a predilection for the anogenital region. Although they are readily transmitted, and most are transient, they can cause disease that manifests as genital warts (GW) and squamous intraepithelial lesions on cervical Pap screenings, and high-risk types are the cause of anogenital cancers. HPV types 6 and 11 alone are estimated to cause most viral sexually transmitted infections [4,5]. GW can be exophytic, confluent, cauliflower-like tumors, and their typical morphologies can aid in diagnosis, although they can also be flat or atypical [6,7,8].

To date, few studies have focused on HPV prevalence and related disease among men and women residing in South Korea. The study, conducted among South Korean women, observed a low-risk HPV prevalence of 10.3% among those ages 20-29 years and 3.2% among women ages 50-59 years [9]. While another study observed an overall GW prevalence in South Korea of 0.7% [10].

Studies have shown that GW infection can have a tremendous psychosocial impact on patients [11, 12, 13]. Some of the highest rates of GW occur in adolescents and young adults at a time when individuals are particularly impacted by the stigma associated with a visible sexually transmitted infection (STI). Several key emotions have been identified in GW patients including anger, disgust, shame, embarrassment, depression, anxiety, worry and a feeling of being less desirable, which all can have an impact on sexual relationships [14]. In 1998, research by Maw *et al.* found that up to two-thirds of male and female GW patients made lifestyle changes that impacted their relationships [15].

Recognizing the profound impact that GW and other HPV-related diseases can have on patients has led to the creation of tools to assess the burden of these conditions, including the self-administered HPV Impact Profile (HIP) as developed and validated by Mast *et al.,* the European quality of life (EurQol)-5 dimension (EQ-5D), and the *Cuestionario Específico para Condiloma Acuminado* (CECA; in Spanish) – 'Specific questionnaire for Condylomata Acuminata'. These are standardized and commonly used instruments to measure health-related quality of life (HRQoL). [16,17,18]. The HIP was used in a study of Taiwanese women, and results showed that an abnormal Papanicolaou (Pap) result (including abnormal results and any grade of cervical cancer) has a significant psychosocial impact, and a greater impact for those diagnosed with GW [19]. Pirotta *et al.* also found a significant psychosocial impact on Australian women screened for and diagnosed with an HPV-related disease [20]. These women were found to be more likely to have their social lives disrupted, even more so than those being treated for high-grade cervical dysplasia [20].

Literature on the psychosocial impact of GW in South Korea is scarce. Most available research in the country focuses on cervical cancer, HPV knowledge and attitudes, or intention toward HPV vaccination [21,22,23]. The aim of this study was to evaluate the psychosocial burden of HPV-related diseases, including GW, in South Korea among male and female patients ages 20-60 years.

Materials and Methods

Study Design

A cross-sectional study was conducted from July 28, 2011 to November 30, 2011 in five major cities of South Korea: Seoul, Busan, Daegu, Kwangju, and Daejeon (Appendix Table A-1). The study targeted clinics where cervical cytology screenings, including GW screenings, were performed, and where men and women were seen for HPV-related diseases. The study was approved by the National Evidence-based Health Care Collaborating Agency (NECA), Borame University Hospital, the SMG-SNU University Medical Center, and the Ewha 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 an Intercontinental Marketing Services (IMS) database, a database of nationwide clinics published by Health Insurance Review and Assessment (HIRA). This database includes information pertaining to 5,098 clinics in the five targeted cities (Appendix Table A-2). All data collection for this study was conducted in the office or clinic of the participating physicians.

Patient and Public Involvement

Participant physicians invited their patients for study participation as part of routine practice by asking their patients if they were willing to participate in a one-time survey and giving them a

patient informed consent form with a short description of the survey. The physician provided verification on the survey regarding to which group the patient belonged (GW or control group) and administered the survey in the physician's office. Once the survey was completed, the patient's survey was placed in a sealed envelope and left at the physician's office to be sent or picked up by a research coordinator. Patients were not involved in the recruitment to and conduct of the study. Physicians were asked to read the corresponding questions to the patients to avoid any misinterpretation of questions. The results will not be disseminated to study participants. The current study was not a randomized controlled trial.

Female Patients

Female patients were included in the study if they were between the ages of 20 and 60 years, experienced an HPV-related event within the past 3 months, were in good self-reported health, and belonged to one of the following categories: a) Abnormal Pap test result with no definitive histology, conforming to the Bethesda Category-2001 category of squamous or glandular cell abnormality (for example: atypical cells of undetermined significance [ASCUS], atypical glandular cells of undetermined significance [AGUS], low-grade squamous intraepithelial lesion [LSIL] or high-grade squamous intraepithelial lesion [HSIL]) and no previous high-risk HPV test performed; b) receipt of positive high-risk HPV DNA test results after an abnormal Pap test, as defined in the previous category; c) diagnosis of external GW or treatment for recurrences; d) histological diagnosis of HPV-related cervical dysplasia cervical lesion (eg, CIN1, CIN2, CIN 3); e) normal Pap result with no abnormal Pap test or definitive therapy within the past year; or f) two or more of the above conditions (not including GW patients) were categorized in the upper level of disease. To enable categorizing of women into discreet disease groups of CIN versus GW,

female patients were excluded from the study if they were diagnosed with GW and had any of the following: precancerous cervical lesions, abnormal Pap and HPV-positive, or abnormal Pap test results.

The control group was selected from the same clinic as the case group. Physicians provided verification on the survey regarding patient groups (GW or control group) and gave them the survey to complete in the physician's office. The physician sample was divided across primary care physicians (general practitioners and internal medicine), obstetrics/gynecologists, urologists, and dermatologists. The control group consisted of patients who have never had GW or received treatment for it or had surgery or therapy in the genital area and included all other patients from a physician's practice or clinic.

Male Patients

Male patients were included in the study if they were between ages 20 and 60 years, in good self-reported physical health, and belonged to one of the following categories: a) newly diagnosed or existing external GW within the past 3 months of study recruitment; and b) patients who had never been diagnosed with GW, prescribed GW treatment or had surgery or therapy in the genital area.

Male and female patients were excluded from the study if they: a) had presence of any other concurrent/active STI; b) were concurrently enrolled in clinical studies of investigational agents; c) had a history of known prior or recent (within 1 year of the enrollment date) HPV vaccination; d) had ongoing alcohol or drug abuse; e) were unable to give informed consent; or f) had presence of any condition, which in the opinion of the investigator could interfere with the evaluation of the study objectives.

Survey Instruments

To measure the psychosocial burden (general health, sexual activity, cervical cancer screening behavior, psychosocial impact, GW experience, socio-demographic information), participants completed the three validated questionnaires; HIP (HPV Impact Profile), CECA (*Cuestionario Específico para Condiloma Acuminado* in Spanish– 'Specific questionnaire for Condylomata Acuminata') and EQ-5D (EuroQol-5 Dimension) surveys, which were translated to the Korean language and culturally pre-tested. Questionnaires were administered by the participating physician after patients were diagnosed with HPV-related disease. A pilot test was conducted using a small sample of physicians representing all four types of study physicians (two per specialty, eight total). This was to ensure that all survey questions and exercises were understood by respondents, and included culturally appropriate information.

HIP is a validated, 29-item self-administered questionnaire, designed to measure the psychosocial impact of HPV-related health conditions in women [15]. The response for each item ranges from 0 (lowest impact) to 10 points (highest impact). Items in the HIP survey were linearly transformed to a 0-100 scale, with higher scores indicating better health. To create scale scores, the mean was computed as the sum of the item scores over the number of items answered to account for missing data. If more than 50% of items on the scale were missing, the score was not computed. To create the total scale score, the mean was computed as the sum of all items over the number of items answered on all scales [24]. The scale uses visual-spatial, numeric, and verbal descriptive anchors to assess subject responses. This survey was adapted for use in male patients in consultation with the original developer and has undergone cognitive testing in the United States. Overall HIP scores are categorized as: no or little impact (mean HIP score <40), moderate impact (between 40 and 70) and heavy psychological impact (mean HIP score >70) [19].

The CECA survey includes 10 questions across two domains: emotional and sexual activity [18,25]. CECA scores range from 0 (worst HRQoL) to 100 (best HRQoL). The EQ-5D survey is a two-part questionnaire, including descriptive and thermometer or visual analog scale (VAS), and serves as a generic validated instrument for use as a measure of HRQoL [26]. VAS scores range from 0 (death) to 100 (perfect health).

Statistical Analysis

All study outcomes were summarized descriptively. A descriptive analysis of the EQ-5D questionnaire was performed and numbers and percentages were provided. The Japanese version of the EQ-5D Instrument was used in this study to estimate the utilities associated with EQ-5D health status [27]. Japan was the first Asian country to develop its own preference EQ-5D weights in 2002. The model was chosen to represent Asian preference weights [28]. VAS scores and utility values were reported using the mean and standard deviation (SD) of the VAS score. VAS scores ranged from 0 (worst HRQoL) to 100 (best HRQoL), and utility values from 0 (death) to 1 (perfect health).

Scores obtained for male and female patients were compared according to GW diagnosis (in men) and HPV-related disease or GW diagnosis (in female patients). For continuous variables, comparisons were performed using the student t-test or Mann-Whitney U test. In addition, the effect size (mean difference between the two means divided by the *pooled* standard deviation) between groups has been calculated. For categorical variables, differences between the groups were analyzed using the Chi-square or Fisher Exact test depending on patient distribution across response categories.

CECA scores were reported using the mean, SD, and 95% confidence interval (CI). Student t-tests were performed to compare CECA scores according to gender.

Results

Socio-demographic and Clinical Characteristics

A total of 400 patients participated in the study. Table 1 shows age, marital status, race, highest educational degree, and sexual activity according to gender and HPV diagnosis status. Approximately half of patients included in the study were age 30-44 years (45.3%), 85.9% were in a committed relationship, 51.6% were married, 2.3% earned an education lower than grade 12 (including vocational studies), 75.7% were employed, and 22.5% had no health insurance or other health care coverage.

Table 1. Socio-demographic Characteristics and Sexual Activity of Survey Participants in South Korea by Gender and GW Diagnosis (men) or HPV-related Diseases (women)

	Men (n=150)			Women (n=250)			
	With GW (n=75)	No GW (n=75)	P-value	HPV Disease (n=200)	No HPV Disease (n=50)	P-value	Overall
Age							
Mean	34.07	37.32	0.0422	34.90	35.56	0.6695	35.28
SD	9.48	9.96		9.63	10.32		9.77
Age group							
20-29 years	26 (34.7%)	19 (25.3%)	0.0194	70 (35.0%)	18 (36.0%)	0.9538	133 (33.3%)
30-44 years	40 (53.3%)	33 (44.0%)		86 (43.0%)	22 (44.0%)		181 (45.3%)
45-60 years	9 (12.0%)	23 (30.7%)		44 (22.0%)	10 (20.0%)		86 (21.5%)
Valid n	75	75		200	50		400
Committed relationship							
Yes	66 (88.0%)	62 (83.8%)	0.4596	170 (85.4%)	44 (88.0%)	0.6398	342 (85.9%)
No	9 (12.0%)	12 (16.2%)		29 (14.6%)	6 (12.0%)		56 (14.1%)
Valid n	75	74		199	50		398
Marital status							
Married	32 (42.7%)	45 (60.8%)	0.0976	98 (49.0%)	31 (62.0%)	0.4302	206 (51.6%)
Widowed/Divorced	1 (1.3%)	1 (1.4%)		9 (4.5%)	2 (4.0%)		13 (3.3%)
Separated	2 (2.7%)			6 (3.0%)	1 (2.0%)		9 (2.3%)
Never married	40 (53.3%)	28 (37.8%)		87 (43.5%)	16 (32.0%)		171 (42.9%)
Valid n	75	74		200	50		399
Highest degree							
Less than grade 12 including vocational education	1 (1.3%)	1 (1.3%)	0.1752	4 (2.0%)	3 (6.0%)	0.1159	9 (2.3%)
High school graduate/GED	18 (24.0%)	11 (14.7%)		67 (33.8%)	21 (42.0%)		117 (29.4%)
Some college/technical school including Associate's degree	12 (16.0%)	6 (8.0%)		54 (27.3%)	7 (14.0%)		79 (19.8%)
Baccalaureate degree	40 (53.3%)	48 (64.0%)		68 (34.3%)	16 (32.0%)		172 (43.2%)
Ever had Sexual intercourse							
Yes	75 (100.0%)	70 (93.3%)	0.0229	198 (99.0%)	46 (92.0%)	0.0038	389 (97.3%)
No		5 (6.7%)		2 (1.0%)	4 (8.0%)		11 (2.8%)
Valid n	75	75		200	50		400
Age at first sexual intercourse							
Mean	20.63	21.93	0.0470	21.92	22.84	0.1847	21.78
SD	3.95	3.79		4.19	4.18		4.11

	Men (n=150)			Women (n=250)			
	With GW (n=75)	No GW (n=75)	P-value	HPV Disease (n=200)	No HPV Disease (n=50)	P-value	Overall
Valid n patients	75	68		196	45		384
Number of sex partners in the last 5 years							
No partners		2 (2.9%)	0.0014	6 (3.0%)	2 (4.3%)	0.6072	10 (2.6%)
1 partner	9 (12.0%)	30 (42.9%)		103 (52.3%)	30 (65.2%)		172 (44.3%)
2-5 partners	47 (62.7%)	25 (35.7%)		65 (33.0%)	13 (28.3%)		150 (38.7%)
6-10 partners	10 (13.3%)	9 (12.9%)		9 (4.6%)			28 (7.2%)
11-15 partners	3 (4.0%)	1 (1.4%)		3 (1.5%)	1 (2.2%)		8 (2.1%)
16-20 partners	1 (1.3%)	2 (2.9%)		4 (2.0%)			7 (1.8%)
21-25 partners	3 (4.0%)			2 (1.0%)			5 (1.3%)
26-50 partners	1 (1.3%)			2 (1.0%)			3 (0.8%)
More than 50 partners	1 (1.3%)	1 (1.4%)		3 (1.5%)			5 (1.3%)
Valid n	75	70		197	46		388
Frequency of condom use							
Never	16 (21.3%)	26 (37.7%)	0.0614	86 (43.7%)	24 (52.2%)	0.2860	152 (39.3%)
Less than half the time	28 (37.3%)	13 (18.8%)		30 (15.2%)	10 (21.7%)		81 (20.9%)
About half the time	10 (13.3%)	12 (17.4%)		31 (15.7%)	3 (6.5%)		56 (14.5%)
Not always but more than half the time	16 (21.3%)	10 (14.5%)		26 (13.2%)	3 (6.5%)		55 (14.2%)
Always	5 (6.7%)	7 (10.1%)		15 (7.6%)	5 (10.9%)		32 (8.3%)
I have not had sexual intercourse in the last 12 months		1 (1.4%)		9 (4.6%)	1 (2.2%)		11 (2.8%)
Valid n	75	69		197	46		387
Sexual partners in lifetime							
Heterosexual partners	74 (100.0%)	70 (100.0%)		198 (100.0%)	46 (100.0%)		388 (100.0%)
Valid n	74	70		198	46		388
Sexual partners in the last 12 months							
Heterosexual partners	74 (100.0%)	69 (100.0%)		194 (100.0%)	46 (100.0%)		383 (100.0%)
Mean	2.57	1.80	0.0829	2.06	1.20	0.2046	2.01
SD	2.81	2.49		4.50	0.63		3.62
Valid n	74	69		194	46		383

GW=genital warts; HPV=human papillomavirus; SD=standard deviation; GED=general educational development

The sexual activity of surveyed patients according to gender and GW or selected HPV-related disease is shown in Table 1. Male GW patients reported a younger age at first intercourse compared to female patients (20.6 [4.0] vs. 21.9 [4.2]), and had a greater number of sexual partners (p=0.0014) than those without GW. A higher percentage of female patients with HPV-related diseases reported having had sexual intercourse compared to those without HPV-related diseases (99.0% vs. 92.0%, p=0.0038). No statistically significant differences were observed for any of the remaining sexual activity questions, as reported in Table 1.

Psychosocial Impact

HIP scores for male and female patients are summarized in Table 2. Significantly higher HIP scores were observed among men with GW compared to those without GW for all domains of the score except for 'control-life impact'. Eighty-five percent of men with GW and 32.0% of men without GW reported a moderate psychological impact (p<0.0001).

Table 2. HIP Questionnaire Scores of Participating Patients by GW and HPV-related Diagnosis in South Korea

	Men (n=150)				Women (n=250)*			
	With GW (n=75)	No GW (n=75)	ES	P-value	HPV Disease (n=200)	No HPV Disease (n=50)	ES	P-value
HIP total score								
Mean	50.90	36.13	1.69	<0.0001	53.37	44.98	0.68	<0.0001
95% CI	(48.8; 53.0)	(34.3; 38.0)			(51.8; 55.0)	(41.4; 48.6)		
Valid n	75	75			199	50		
Worries and concerns								
Mean	49.65	24.25	1.51	<0.0001	57.19	41.94	0.63	<0.0001
95% CI	(45.5; 53.8)	(20.8; 27.7)			(54.2; 60.2)	(35.5; 48.4)		
Valid n	75	75			199	49		
Emotional impact								
Mean	49.10	33.98	1.19	<0.0001	56.08	42.32	0.84	<0.0001
95% CI	(46.0; 52.2)	(31.3; 36.6)			(53.8; 58.4)	(37.8; 46.8)		
Valid n	75	75			199	50		
Sexual impact								
Mean	47.53	41.20	0.51	0.0019	50.81	49.80	0.07	0.6550
95% CI	(45.1; 50.0)	(38.1; 44.3)			(48.9; 52.8)	(45.3; 54.3)		
Valid n	75	75			197	49		
Self-Image								
Mean	49.00	41.63	0.76	<0.0001	47.66	45.17	0.19	0.2226
95% CI	(46.5; 51.5)	(39.8; 43.5)			(45.9; 49.5)	(41.4; 48.9)		

	Men (n=150)				Women (n=250)*			
	With GW (n=75)	No GW (n=75)	ES	P-value	HPV Disease (n=200)	No HPV Disease (n=50)	ES	P-value
Valid n	75	75			199	50		
Partner issues and transmission								
Mean	62.16	42.12	1.40	<0.0001	58.86	47.23	0.62	0.0001
95% CI	(59.1; 65.2)	(38.5; 45.8)			(56.2; 61.5)	(41.8; 52.6)		
Valid n	74	66			185	47		
Interactions with doctors								
Mean	51.31	33.28	0.90	<0.0001	46.75	45.73	0.20	0.6611
95% CI	(47.4; 55.3)	(25.2; 41.4)			(44.8; 48.7)	(40.8; 50.6)		
Valid n	71	30			199	50		
Control - life impact								
Mean	49.69	52.13	0.23	0.1643	48.48	52.37	0.31	0.0641
95% CI	(47.3; 52.0)	(49.6; 54.7)			(46.6; 50.4)	(49.2; 55.5)		
Valid n	75	75			199	50		
HIP total score categorized								
No or little impact	11 (14.7%)	51 (68.0%)		<0.0001	23 (11.5%)	17 (34.0%)		0.0004
Moderate impact	64 (85.3%)	24 (32.0%)			168 (84.0%)	30 (60.0%)		
Heavy psychological impact					9 (4.5%)	3 (6.0%)		
Valid n	75	75			200	50		

* HPV=human papillomavirus is included in this table. GW=genital warts; CI=confidence interval; HIP=human papillomavirus impact profile; ES=Effect size. Effect size (ES) >0.01 is considered significant.
HIP items range from 0 (lowest impact) to 10 point (highest impact).
CECA scores range from 0 (worst HRQL) to 100 (the best HRQL)
EQ-5D range from 0 (worst imaginable health state) to 100 (best imaginable health state)

When comparing women diagnosed with HPV-related disease to those without disease, significant differences were observed for the 'worries and concerns', 'emotional impact', and 'partner's issues and transmission' domains. In all domains, female patients with HPV-related

disease had higher scores, reflecting a higher psychological impact (88.5% of female patients with selected HPV-related diseases vs. 66.0% without reported a moderate or heavy psychological impact [p=0.0004]).

HIP scores by specific HPV-related disease were also conducted. In all domains except for 'control-life impact' and 'emotional impact', significant differences were identified. Higher scores, and thereby higher psychological impact, were reported by patients with external GW. All GW patients had either moderate or heavy psychological impact (90.0% and 10.0%, respectively). In all domains, female patients with selected HPV-related diseases had higher scores, reflecting a higher psychological impact (Appendix Table A-3).

CECA scores stratified by gender are shown in Figure 1. Women with GW reported significantly lower scores on the 'emotional health' (mean [SD], 7.2 [4.2]), and 'sexual activity' dimensions (11.0 [5.8]) compared to men with GW – 'emotional health' dimension (10.5 [3.8]) and 'sexual activity' dimension (15.9 [6.1]) – indicating worse HRQoL among women.

No significant differences were observed for problems reported by male patients in the EQ-5D descriptive system by GW diagnosis, as most male patients reported no problems. Among those who reported problems, the most frequent were 'pain-discomfort' (10.7%) and 'anxiety-depression' (12.7%, Table 3). Female patients with selected HPV-related diseases reported more problems related to the EQ-5D 'anxiety-depression' dimension than those without. Thirty-one percent of those with selected HPV-related diseases reported feeling moderately or extremely anxious or depressed, compared to 10.0% of female patients without HPV-related diseases. There were no statistically significant differences in the remaining EQ-5D items between female patients with and without HPV-related diseases (Table 3).

Table 3. EQ-5D Descriptive System Results by Male and Female patients with and without GW and Selected HPV-related Diseases in South Korea

	Men (n=150)			Women (n=250)		
	With GW (n=75)	No GW (n=75)	P-value	HPV Disease (n=200)	No HPV Disease (n=50)	P-value
Mobility						
I have no problems walking about	73 (97.3%)	75 (100.0%)	0.1545	193 (97.0%)	49 (98.0%)	0.6979
I have some problems walking about	2 (2.7%)			6 (3.0%)	1 (2.0%)	
Valid n	75	75		199	50	
Self-Care						
I have no problems with self-care	75 (100.0%)	75 (100.0%)	--	197 (99.0%)	50 (100.0%)	0.7762
I have some problems washing or dressing myself				1 (0.5%)		
I am unable to wash or dress myself				1 (0.5%)		
Valid n	75	75		199	50	
Usual Activities						
I have no problems with performing my usual activities	72 (96.0%)	75 (100.0%)	0.0802	196 (98.5%)	49 (98.0%)	0.8044
I have some problems with performing my usual activities	3 (4.0%)			3 (1.5%)	1 (2.0%)	
Valid n	75	75		199	50	
Pain - Discomfort						
I have no pain or discomfort	65 (86.7%)	69 (92.0%)	0.2900	165 (82.9%)	40 (80.0%)	0.6291
I have moderate pain or discomfort	10 (13.3%)	6 (8.0%)		34 (17.1%)	10 (20.0%)	
Valid n	75	75		199	50	
Anxiety - Depression						
I am not anxious or depressed	66 (88.0%)	65 (86.7%)	0.8061	136 (68.3%)	45 (90.0%)	0.0078
I am moderately anxious or depressed	9 (12.0%)	10 (13.3%)		56 (28.1%)	5 (10.0%)	
I am extremely anxious or depressed				7 (3.5%)		
Valid n	75	75		199	50	

EQ-5D=EuroQol-5 Dimension; GW=genital warts; HPV=human papillomavirus; SD=standard deviation
'HIP items range from 0 (lowest impact) to 10 point (highest impact).
CECA scores range from 0 (worst HRQL) to 100 (the best HRQL)
EQ-5D range from 0 (worst imaginable health state) to 100 (best imaginable health state)

EQ-5D descriptive system responses were also compared among female patients by HPV-related disease (Appendix Table A-4). The only two dimensions with significant differences were 'pain/discomfort' (p=0.0146) and 'anxiety/depression' (p=0.0387). A higher percentage of female GW patients reported being 'moderately anxious or depressed' and 'extremely anxious or depressed' (48.0%), followed by those with precancerous lesions (34.7%) and those presenting abnormal Pap test and HPV positive results (24.0%) (Appendix TableA- 4).

Table 4 shows VAS scores and utility values obtained from male participants according to GW diagnosis. Those patients with GW reported significantly lower mean VAS scores (75.3) than those without (81.1, p=0.0135). No significant differences in utility values according to GW diagnosis were identified.

Table 4 EQ-5D VAS Scores and Utility Values by Male Patients with and without GW and Female Patients with and without Selected HPV-related Disease in South Korea

	Men (n=150)					Women (n=250)				
	With GW (n=75)	No GW (n=75)	ES	P-value	Overall	HPV disease (n=200)	No HPV disease (n=50)	ES	P-value	Overall
VAS (EQ-5D)										
Mean	75.31	81.13	0.41	0.0135	78.16	72.18	76.86	0.30	0.0606	73.14
95% CI	(71.6; 79.0)	(78.4; 83.9)			(75.8; 80.5)	(69.9; 74.4)	(72.6; 81.1)			(71.2; 75.1)
Valid n	74	71			145	190	49			239
Utility values										
Mean	0.95	0.95	<0.01	0.7527	0.95	0.90	0.94	0.27	0.0773	0.91
95% CI	(0.9; 1.0)	(0.9;			(0.9; 1.0)	(0.9; 0.9)	(0.9; 1.0)			(0.9; 0.9)
Valid n	75	75			150	199	50			249

HPV = human papillomavirus; GW = genital warts; CI = confidence interval; EQ-5D = EuroQol-5 Dimension; ES = Effect size. Effect size (ES) >0.01 is considered significant.

'HIP items range from 0 (lowest impact) to 10 point (highest impact).
CECA scores range from 0 (worst HRQL) to 100 (the best HRQL)
EQ-5D range from 0 (worst imaginable health state) to 100 (best imaginable health state)

Female patients with selected HPV-related diseases showed numerically lower mean VAS scores (72.2) and utility values (0.90) than those without selected HPV-related diseases (76.86 and 0.94, respectively), but the differences were not significant. When comparing selected HPV-related diseases, the lowest VAS and utility scores (worst HRQoL) were observed in GW patients ($p<0.0001$, Appendix Table A-5).

Discussion

This cross-sectional study estimated the psychosocial burden of GW and HPV related diseases in South Korea by obtaining self-reported HPV disease-related information among male and female patients age 20-60 years presenting to clinics where cervical cytology screenings, including GW screenings, were performed, and where men and women were seen for HPV-related diseases. To our knowledge, this is the first study that has looked at the psychosocial burden of GW and HPV-related disease on patients' quality of life in South Korea. Higher HIP score values, reflecting a greater psychosocial impact of the disease, were recorded for men with GW than for those without GW (50.90 vs. 36.13) and in women diagnosed with HPV-related diseases than for those without (53.37 vs. 44.98).

Overall, female patients had a greater psychosocial impact compared to male patients (HIP scores: 51.69 vs. 43.51). Similarly, male patients had better HRQoL indicating lower psychosocial impact compared to female patients, as assessed by CECA scores (6.33 vs. 4.34). VAS scores

ranged from 0 (worst imaginable health status) to 100 (best imaginable health status), and female patients reported worse health status (73.14) compared to male patients (78.16), particularly female patients with HPV-related diseases (72.18). In addition, GW patients reported worse HRQoL scores compared to those without GW in the disease-specific HIP questionnaire. Furthermore, women reported poorer health status following a GW diagnosis than a CIN diagnosis. These results are consistent with a Chinese study by Wang *et al* [29] which reported that female GW patients had the highest mean HIP scores (52.2), showing a significant psychological impact, followed by patients with precancerous cervical lesions (48.6), HPV after abnormal Pap test results (45.8), abnormal Pap test results without HPV test (44.1), and HPV after abnormal Pap test results (43.1).

In the current study, HRQoL results suggest that GW in males and HPV-related disease (high-grade dysplasia requiring ablation treatment) in female patients had a negative impact on patient well-being and HRQoL scores. This study also observed that female GW patients suffered a major impact compared to those with other selected HPV-related diseases. Previous studies have shown that patients with GW had significantly lower quality of life, and substantial psychosocial burden with higher social stigma – especially when GW infection is symptomatic, visible to the naked eye, and found in the genital region [30,31,32]. In addition, a study that compared GW patients with asymptomatic genitourinary internal medicine patients observed that patients with GW had a significantly higher psychological burden because of the GW infection compared to the other patients. The study also observed that infection with GW not only influences the patient's physical wellbeing but also has a potentially detrimental effect on the patient's emotions [33]. This could explain the observed poorer health status in GW patients evaluated in this study. Furthermore, the highest score was in the 'partner issue and transmission' category, followed by 'worries and concerns' and 'emotional impact', with a HIP mean score >60. The lowest scores

were in the 'control-life impact' category (mean HIP score 45.20). A similar study using the HIP survey instrument in Australia found that the largest impact of GW on quality of life was in the domains of 'sexual impact', 'self-image,' and 'partner and transmission' [24].

Based on EQ-5D survey results, GW and selected HPV-related disease patients reported more problems related to 'anxiety-depression' than those without these conditions. The current study detected a lower impact of GW as assessed by EQ-5D than in the previous Canadian study [34]. HRQoL scores in each of the questionnaires reported by female study patients were descriptively compared among the study subgroups (abnormal Pap result, abnormal Pap and HPV positive results, precancerous lesions, and external GW). While GW has an impact on HRQoL in the current study, the precise impact is difficult to assess due to scarcity of data and the heterogeneity of the instruments used to compare scores of GW patients with those of the general population [35].

Shin *et al.* conducted a similar study in mainland China in 2012 and found that 56.4% of patients reported some problems in the 'anxiety and depression' dimension (highest), followed by 'pain and discomfort' (24.7%) and 'mobility' (3.5%) [16]. In a study from the United Kingdom in 2008, Woodhall *et al.* found that female GW patients had lower VAS and EQ-5D index scores than control patients, even after adjusting for age and gender. The difference was particularly notable in young women [36]. Consistent with the current study results, Woodhall *et al.* also reported that the 'pain and discomfort' and 'depression and anxiety' dimensions were the two most affected domains.

This study also observed that 60% of women with no GW reported a moderate impact in the HIP scoring. Reasons for this impact level among these patients were not evaluated. However,

there is the possibility that these patients may have had other conditions during presentation at the clinic that may have impacted their HIP score.

Overall, the results of the current study suggest that a GW diagnosis has a great psychosocial impact on female patients. Other studies have provided evidence that the psychosocial impact of sexually transmitted disease diagnoses may be greater for women than for men. The origin of these differences is not clear, but they may be due to sexual infectivity and reproductive health [36]. Furthermore, research among women who received abnormal cervical smear test results have indicated that they often experienced psychosocial consequences including anxiety, fears about cancer, sexual difficulties, changes in body image and concerns regarding loss of reproductive function [13,37]. Shi *et al.* also indicated in their study that culture plays an important role, as conservative cultures (such as South Korea) view a diagnosis of a sexually transmitted disease such as GW as disgraceful. Consequently, patients would not seek support, even from their own families [16]. Additionally, continued study of HPV natural history among men from different geographic regions is necessary to elucidate the underlying HPV-related diseases occurring in these populations.

Limitations

The current study is limited, as selection bias may have occurred due to the convenience sample approach used. The data were collected in participating physician offices and clinics through questionnaires and interview-based surveys. Patients may have given expected rather than truthful answers, which may not give the true psychosocial impact. Moreover, only patients who sought professional GW treatment were included in the study, which may not be generalizable to the entire South Korean GW population. As the study was cross-sectional in design, it can only

report the impact of GW on the patients at the time the survey was taken, rather than longer-term impact. However, in a longitudinal study conducted to determine the impact of HPV status on quality of life (QoL) in oral cavity and oropharyngeal squamous cell carcinoma, results showed that QoL scores were lower in HPV positive patients. [38] The study design is a simple descriptive comparison of outcomes, so potential factors that might mediate or moderate the psychosocial effects of GW were not evaluated. We recommend that for future studies on GW in South Korea, multivariate analysis be carried out to address these factors.

Conclusion

The diagnosis of GW, a common sexually transmitted disease, has significant associated morbidity – largely due to the psychosocial impact GW have on patients. Prevention of all HPV-related diseases, cancers, and non-cancerous lesions is important. Vaccines that have broad protection against multiple HPV types should be considered. In addition, the results of this study can help direct guidelines for patient counseling and health education and emphasize the need to include HPV vaccine programs as a part of national vaccine programs. The purpose of this study was to determine the psychosocial impact of GW among male and female patients in South Korea utilizing various validated tools, given that literature related to the psychosocial impact of GW is scarce in this country. The current study results, utilizing HRQoL, suggest that GW in males and high-grade dysplasia requiring ablation treatment in female patients have a negative impact on patient well-being and HRQoL. The psychosocial burden was particularly greater among female GW patients compared to those with other selected HPV-related disease.

Although recent studies have looked at the psychosocial impact of GW on HRQoL in other places like China, [11] Singapore, [12] and the UK, [13] this study highlights the psychosocial impact of GW on HRQoL for infected patients in South Korea. Previously published studies used

for comparison to the results of this study vary substantially in methodology and are different in nature due to the dissimilarities of GW across regions and cultures. However, the current study offers baseline data, and further research is encouraged to measure the psychosocial burden of GW in South Korea. Despite its limitations, the current study offers groundwork for measurement of the psychosocial impact of GW in South Korea that was previously unavailable.

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.

Funding

This study was funded by Merck and Co.

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.

Data Sharing Agreement

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

Supporting Information

Figure Legends

Figure 1. CECA Questionnaire Scores by Male and Female Patients with GW in South Korea

CECA=*Cuestionario Específico para Condiloma Acuminado* (in Spanish) – 'Specific questionnaire for Condylomata Acuminata'; GW=genital warts

Participating Physicians by Region in South Korea

DERM=dermatologist; OBGYN=obstetrician/gynecologist; PCP=primary care physician; URO=urologist

Table A-1. Target Number Of Clinics Within A Specialty Per City in South Korea

Table A-2. Participating Physicians by Region in South Korea

Table A-3. HIP Questionnaire Scores by Female Patients and selected HPV-related diseases in South Korea

HPV=human papillomavirus; HIP=HPV impact profile; Pap=Papanicolaou test; GW=genital warts; CI=confidence interval

Table A-4. EQ-5D Descriptive System Results by Female Patients and selected HPV-related Diseases in South Korea (excluding control group)

EQ-5D=EuroQol-5 Dimension; HPV=human papillomavirus; Pap=Papanicolaou test; GW=genital warts

Table A-5. EQ-5D VAS and Utility Scores for Female Patients by selected HPV-related Diseases in South Korea (excluding control group)

EQ-5D=EuroQol-5 Dimension; VAS=visual analog scores; HPV=human papillomavirus; Pap=Papanicolaou test; GW=genital warts; CI=confidence interval

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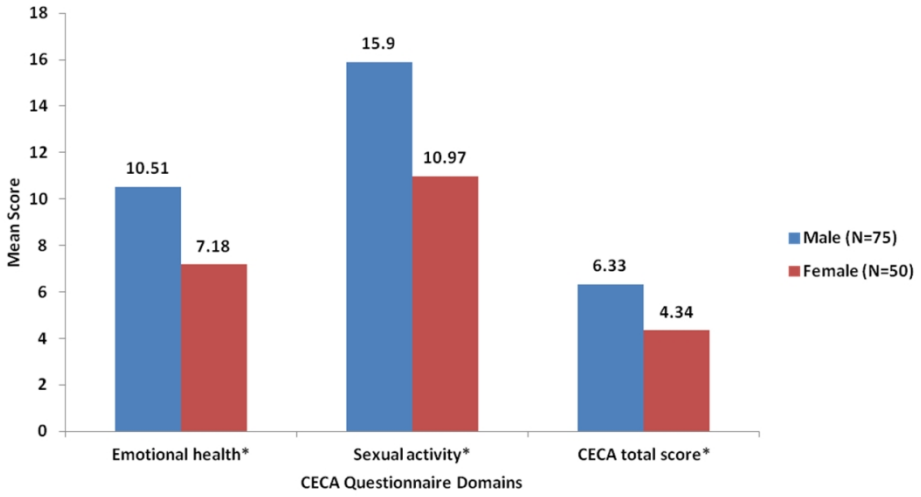

Figure 1. CECA Questionnaire Scores by Male and Female Patients with GW in South Korea / CECA=Cuestionario Específico para Condiloma Acuminado (in Spanish) – 'Specific questionnaire for Condylomata Acuminata'; GW=genital warts

364x193mm (96 x 96 DPI)

APPENDIX

Table A-1. Participating Physicians by Region in South Korea

	PCP (n=50)	DERM (n=35)	OB/GYN (n=65)	URO (n=50)	Overall (n=200)
Region					
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

DERM=dermatologist; OBGYN=obstetrician/gynecologist; PCP=primary care physician; URO=urologist

Table A-2. Target Number Of Clinics Within A Specialty Per City in South Korea

City	OB/GYN	URO	DERM	PCP	Overall	
	N	N	N	N	N	%
Seoul	37	24	20	31	112	60%
Busan	9	8	4	8	29	15%
Daegu	7	7	3	4	21	11%
Kwangju	4	4	2	3	13	7%
Daejeon	4	4	1	4	13	7%
Total	61	47	30	50	188	100%

Table A-3. HIP Questionnaire Scores by Female Patients and selected HPV-related diseases in South Korea

	HPV Disease (n=200)					
	Abnormal Pap (n=50)	Abnormal Pap and HPV positive (n=50)	Precancerous Lesions (n=50)	External GW (n=50)	No HPV Disease (n=50)	Overall
HPV Impact Profile total						
Mean	50.54	52.59	50.69	59.61	44.98	51.69
95% CI	(47.0;	(49.4;	(47.6; 53.8)	(57.2;	(41.4;	(50.2; 53.2)
Valid n	50	50	49	50	50	249
HPV Impact Profile total						
No or little impact	9 (18.0%)	7 (14.0%)	7 (14.0%)		17	40 (16.0%)
Moderate impact	40 (80.0%)	41 (82.0%)	42 (84.0%)	45	30	198
Heavy psychological	1 (2.0%)	2 (4.0%)	1 (2.0%)	5 (10.0%)	3 (6.0%)	12 (4.8%)
Valid n	50	50	50	50	50	250
Worries and concerns						
Mean	52.64	54.20	54.73	67.14	41.94	54.18
95% CI	(46.0;	(48.2;	(49.3; 60.1)	(61.8;	(35.5;	(51.4; 57.0)
Valid n	50	50	49	50	49	248
Emotional impact						
Mean	53.16	56.24	54.37	60.52	42.32	53.32
95% CI	(48.8;	(51.2;	(49.6; 59.2)	(56.3;	(37.8;	(51.2; 55.5)
Valid n	50	50	49	50	50	249
Sexual impact						
Mean	49.30	48.85	51.73	53.30	49.80	50.61
95% CI	(45.7;	(45.6;	(46.6; 56.9)	(49.8;	(45.3;	(48.8; 52.4)
Valid n	50	48	49	50	49	246
Self-Image						
Mean	46.85	49.25	40.20	54.20	45.17	47.16
95% CI	(43.1;	(45.9;	(36.8; 43.6)	(51.2;	(41.4;	(45.5; 48.8)
Valid n	50	50	49	50	50	249
Partner issues and transmission						
Mean	55.42	57.73	51.71	70.07	47.23	56.51
95% CI	(50.0;	(52.5;	(45.8; 57.6)	(66.4;	(41.8;	(54.1; 59.0)
Valid n	48	47	43	47	47	232
Interactions with doctors						
Mean	42.47	47.33	46.26	50.93	45.73	46.55
95% CI	(38.7;	(43.5;	(42.4; 50.1)	(46.8;	(40.8;	(44.7; 48.4)
Valid n	50	50	49	50	50	249
Control - life impact						
Mean	49.33	49.73	49.66	45.20	52.37	49.26
95% CI	(45.5;	(46.3;	(45.9; 53.4)	(40.7;	(49.2;	(47.6; 50.9)

	HPV Disease (n=200)					
	Abnormal Pap (n=50)	**Abnormal Pap and HPV positive (n=50)**	**Precancerous Lesions (n=50)**	**External GW (n=50)**	**No HPV Disease (n=50)**	**Overall**
Valid n	50	50	49	50	50	249

HPV=human papillomavirus; HIP=HPV impact profile; Pap=Papanicolaou test; GW=genital warts; CI=confidence interval

Table A-4. EQ-5D Descriptive System Results by Female Patients and selected HPV-related Diseases in South Korea (excluding control group)

	Abnormal Pap Result (n=50)	Abnormal Pap Result and HPV positive (n=50)	Precancerous Lesions (n=50)	External GW (n=50)	Overall	P-value
Mobility						
I have no problems walking about	49 (98.0%)	50 (100.0%)	47 (95.9%)	47 (94.0%)	193 (97.0%)	0.3403
I have some problems walking about	1 (2.0%)		2 (4.1%)	3 (6.0%)	6 (3.0%)	
Valid n	50	50	49	50	199	
Self-Care						
I have no problems with self-care	50 (100.0%)	50 (100.0%)	48 (98.0%)	49 (98.0%)	197 (99.0%)	0.6193
I have some problems washing or dressing myself				1 (2.0%)	1 (0.5%)	
I am unable to wash or dress myself			1 (2.0%)		1 (0.5%)	
Valid n	50	50	49	50	199	
Usual Activities						
I have no problems with performing my usual activities	50 (100.0%)	50 (100.0%)	47 (95.9%)	49 (98.0%)	196 (98.5%)	0.1960
I have some problems with performing my usual activities			2 (4.1%)	1 (2.0%)	3 (1.5%)	
Valid n	50	50	49	50	199	
Pain - Discomfort						
I have no pain or discomfort	46 (92.0%)	43 (86.0%)	42 (85.7%)	34 (68.0%)	165 (82.9%)	0.0146
I have moderate pain or discomfort	4 (8.0%)	7 (14.0%)	7 (14.3%)	16 (32.0%)	34 (17.1%)	
Valid n	50	50	49	50	199	
Anxiety - Depression						
I am not anxious or depressed	40 (80.0%)	38 (76.0%)	32 (65.3%)	26 (52.0%)	136 (68.3%)	0.0387
I am moderately anxious or depressed	10 (20.0%)	10 (20.0%)	15 (30.6%)	21 (42.0%)	56 (28.1%)	
I am extremely anxious or depressed		2 (4.0%)	2 (4.1%)	3 (6.0%)	7 (3.5%)	
Valid n	50	50	49	50	199	

EQ-5D=EuroQol-5 Dimension; HPV=human papillomavirus; Pap=Papanicolaou test; GW=genital warts

Table A-5. EQ-5D VAS and Utility Scores for Female Patients by selected HPV-related Diseases in South Korea (excluding control group)

	Abnormal Pap (n=50)	Abnormal Pap and HPV positive (n=50)	Precancerous Lesions (n=50)	External GW (n=50)	Overall	p-value
VAS (EQ-5D)						
Mean	74.51	73.78	71.50	68.92	72.18	<0.0001
95% CI	(69.8; 79.2)	(70.0; 77.6)	(66.5; 76.5)	(64.2; 73.6)	(69.9; 74.4)	
Valid n	49	49	42	50	190	
Utility values						
Mean	0.94	0.93	0.89	0.85	0.90	<0.0001
95% CI	(0.9; 1.0)	(0.9; 1.0)	(0.9; 0.9)	(0.8; 0.9)	(0.9; 0.9)	
Valid n	50	50	49	50	199	

EQ-5D=EuroQol-5 Dimension; VAS=visual analog scores; HPV=human papillomavirus;

Pap=Papanicolaou test; GW=genital warts; CI=confidence interval

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. 3**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **– Pg. 3**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **–Pg. 5-6**
Objectives	3	State specific objectives, including any prespecified hypotheses – **Pg. 6**
Methods		
Study design	4	Present key elements of study design early in the paper – **Pg. 7-11**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – **Pgs. 7-11**
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. 7-11**
		(*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. 10-11**
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. 10-11**
Bias	9	Describe any efforts to address potential sources of bias – **Pg. 22**
Study size	10	Explain how the study size was arrived at – **Pg. 7-11**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why – **Pg. 9-11**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding – **Pgs. 10-11**
		(*b*) Describe any methods used to examine subgroups and interactions – **Pg. 8-10**
		(*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. 7-11**
		(*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. 11 - 12**
		(b) Give reasons for non-participation at each stage – **Pgs. 7-9**
		(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. 7-9, 11-13**
		(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. 15-20**
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 – **N/A**
		(*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. 11-20**
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. 22-23**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence – **Pgs. 20-22**
Generalisability	21	Discuss the generalisability (external validity) of the study results – **Pgs. 20-22**
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. 1**

*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.