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

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Keywords:	genital warts, psychosocial impact, South Korea

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Manuscripts

Taek Sang Lee

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

3 **Short Title:** GW: Psychosocial Impact in South Korea

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18 **Keywords:** Genital Warts, Psychosocial impact, South Korea

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20 Research, for medical writing assistance.

18 Abstract

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

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

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

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

31 **Results:** Of 150 male and 250 female patients, HIP scores showed 85.3% of male patients with
32 genital warts (GW) and 32.0% without reported moderate psychological impact ($p<0.0001$). In
33 categorized total scores, 88.5% of female patients with and 66.0% without selected HPV-related
34 diseases reported moderate or high psychological impacts ($p=0.0004$). In the CECA
35 questionnaire, male patients had mean (standard deviation) scores of 10.51 (3.79) in ‘emotional
36 health’, and 15.90 (6.13) in ‘sexual activity’. Female patients with GW reported lower scores in
37 both dimensions with mean scores of 7.18 (4.17) in ‘emotional health’ and 10.97 (5.80) in
38 ‘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.

56 Introduction

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

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

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

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4 78 Recognizing the profound impact that GW and other HPV-related diseases can have on
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7 79 patients has led to the creation of tools to assess the burden of these conditions, including the
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9 80 self-administered HPV Impact Profile (HIP) as developed and validated by Mast *et al.*, the
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11 81 European quality of life (EurQol)-5 dimension (EQ-5D), and the *Cuestionario Especifico para*
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13 82 *Condiloma Acuminado* (CECA; in Spanish) – ‘Specific questionnaire for Condylomata
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15 83 *Acuminata*’. These are standardized and commonly used instruments to measure health-related
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17 84 quality of life (HRQoL). [16,17,18]. The HIP was used in a study of Taiwanese women, and
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19 85 results showed that an abnormal Papanicolaou (Pap) result (including abnormal results and any
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21 86 grade of cervical cancer) has a significant psychosocial impact, and a greater impact for those
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23 87 diagnosed with GW [19]. Pirotta *et al.* also found a significant psychosocial impact on Australian
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25 88 women screened for and diagnosed with an HPV-related disease [20]. These women were found
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27 89 to be more likely to have their social lives disrupted, even more so than those being treated for
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29 90 high-grade cervical dysplasia [20].
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34 91 Literature on the psychosocial impact of GW in South Korea is scarce. Most available
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36 92 research in the country focuses on cervical cancer, HPV knowledge and attitudes, or intention
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38 93 toward HPV vaccination [21,22,23]. The aim of this study was to evaluate the psychosocial
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40 94 burden of HPV-related diseases, including GW, in South Korea among male and female patients
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43 95 ages 20-60 years.
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97 **Materials and Methods**

98 *Study Design*

99 A cross-sectional study was conducted from July 28, 2011 to November 30, 2011 in five
100 major cities of South Korea: Seoul, Busan, Daegu, Kwangju, and Daejeon (Appendix Table A-
101 1). The study targeted clinics where cervical cytology screenings, including GW screenings,
102 were performed, and where men and women were seen for HPV-related diseases. The study was
103 approved by the National Evidence-based Health Care Collaborating Agency (NECA), Borame
104 University Hospital, the SMG-SNU University Medical Center, and the Ewha University
105 Mokdong Hospital ethics committees. No confidential patient-level data was collected for this
106 study.

107 *Inclusion and Exclusion Criteria*

108 Participating Physicians

109 Participating physicians were identified through an Intercontinental Marketing Services
110 (IMS) database, a database of nationwide clinics published by Health Insurance Review and
111 Assessment (HIRA). This database includes information pertaining to 5,098 clinics in the five
112 targeted cities (Appendix Table A-2). All data collection for this study was conducted in the
113 office or clinic of the participating physicians.

114 Patient and Public Involvement

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

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4 117 patient informed consent form with a short description of the survey. The physician provided
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6 118 verification on the survey regarding to which group the patient belonged (GW or control group)
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9 119 and administered the survey in the physician's office. Once the survey was completed, the
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11 120 patient's survey was placed in a sealed envelope and left at the physician's office to be sent or
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13 121 picked up by a research coordinator. Patients were not involved in the recruitment to and conduct
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16 122 of the study. Physicians were asked to read the corresponding questions to the patients to avoid
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18 123 any misinterpretation of questions. The results will not be disseminated to study participants.
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21 124 The current study was not a randomized controlled trial.

22 23 24 125 Female Patients

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27 126 Female patients were included in the study if they were between the ages of 20 and 60
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29 127 years, experienced an HPV-related event within the past 3 months, were in good self-reported
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31 128 health, and belonged to one of the following categories: a) Abnormal Pap test result with no
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33 129 definitive histology, conforming to the Bethesda Category-2001 category of squamous or
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35 130 glandular cell abnormality (for example: atypical cells of undetermined significance [ASCUS],
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37 131 atypical glandular cells of undetermined significance [AGUS], low-grade squamous
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39 132 intraepithelial lesion [LSIL] or high-grade squamous intraepithelial lesion [HSIL]) and no
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41 133 previous high-risk HPV test performed; b) receipt of positive high-risk HPV DNA test results
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43 134 after an abnormal Pap test, as defined in the previous category; c) diagnosis of external GW or
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45 135 treatment for recurrences;
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49 136 d) histological diagnosis of HPV-related cervical dysplasia cervical lesion (eg, CIN1, CIN2, CIN
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52 137 3); e) normal Pap result with no abnormal Pap test or definitive therapy within the past year; or f)
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55 138 two or more of the above conditions (not including GW patients) were categorized in the upper
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4 139 level of disease. To enable categorizing of women into discreet disease groups of CIN versus
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7 140 GW, female patients were excluded from the study if they were diagnosed with GW and had any
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9 141 of the following: precancerous cervical lesions, abnormal Pap and HPV-positive, or abnormal
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11 142 Pap test results.
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14 143 The control group was selected from the same clinic as the case group. Physicians
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16 144 provided verification on the survey regarding patient groups (GW or control group) and gave
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18 145 them the survey to complete in the physician's office. The physician sample was divided across
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20 146 primary care physicians (general practitioners and internal medicine), obstetrics/gynecologists,
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22 147 urologists, and dermatologists. The control group consisted of patients who have never had GW
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24 148 or received treatment for it or had surgery or therapy in the genital area and included all other
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26 149 patients from a physician's practice or clinic.
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31 Male Patients

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34 151 Male patients were included in the study if they were between ages 20 and 60 years, in
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36 152 good self-reported physical health, and belonged to one of the following categories: a) newly
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38 153 diagnosed or existing external GW within the past 3 months of study recruitment; and b) patients
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40 154 who had never been diagnosed with GW, prescribed GW treatment or had surgery or therapy in
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42 155 the genital area.
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46 156 Male and female patients were excluded from the study if they: a) had presence of any
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48 157 other concurrent/active STI; b) were concurrently enrolled in clinical studies of investigational
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50 158 agents; c) had a history of known prior or recent (within 1 year of the enrollment date) HPV
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52 159 vaccination; d) had ongoing alcohol or drug abuse; e) were unable to give informed consent; or f)
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4 160 had presence of any condition, which in the opinion of the investigator could interfere with the
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7 161 evaluation of the study objectives.
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10 162 *Survey Instruments*

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12 163 To measure the psychosocial burden (general health, sexual activity, cervical cancer
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14 164 screening behavior, psychosocial impact, GW experience, socio-demographic information),
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17 165 participants completed the three validated questionnaires; HIP (HPV Impact Profile), CECA
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19 166 (*Cuestionario Especifico para Condiloma Acuminado* in Spanish– ‘Specific questionnaire for
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21 167 Condylomata Acuminata’) and EQ-5D (EuroQol-5 Dimension) surveys, which were translated to
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24 168 the Korean language and culturally pre-tested. Questionnaires were administered by the
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26 169 participating physician after patients were diagnosed with HPV-related disease. A pilot test was
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28 170 conducted using a small sample of physicians representing all four types of study physicians
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31 171 (two per specialty, eight total). This was to ensure that all survey questions and exercises were
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33 172 understood by respondents, and included culturally appropriate information.
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35 173 HIP is a validated, 29-item self-administered questionnaire, designed to measure the
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37 174 psychosocial impact of HPV-related health conditions in women [15]. The response for each
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40 175 item ranges from 0 (lowest impact) to 10 points (highest impact). Items in the HIP survey were
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42 176 linearly transformed to a 0-100 scale, with higher scores indicating better health. To create scale
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44 177 scores, the mean was computed as the sum of the item scores over the number of items answered
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47 178 to account for missing data. If more than 50% of items on the scale were missing, the score was
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49 179 not computed. To create the total scale score, the mean was computed as the sum of all items
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51 180 over the number of items answered on all scales [24]. The scale uses visual-spatial, numeric, and
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54 181 verbal descriptive anchors to assess subject responses. This survey was adapted for use in male
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56 182 patients in consultation with the original developer and has undergone cognitive testing in the
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4 183 United States. Overall HIP scores are categorized as: no or little impact (mean HIP score <40),
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6 184 moderate impact (between 40 and 70) and heavy psychological impact (mean HIP score >70)
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9 185 [19].
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11 186 The CECA survey includes 10 questions across two domains: emotional and sexual
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13 187 activity [18,25]. CECA scores range from 0 (worst HRQoL) to 100 (best HRQoL). The EQ-5D
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15 188 survey is a two-part questionnaire, including descriptive and thermometer or visual analog scale
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17 189 (VAS), and serves as a generic validated instrument for use as a measure of HRQoL [26]. VAS
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19 190 scores range from 0 (death) to 100 (perfect health).
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24 191 *Statistical Analysis*

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27 192 All study outcomes were summarized descriptively. A descriptive analysis of the EQ-5D
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29 193 questionnaire was performed and numbers and percentages were provided. The Japanese version
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31 194 of the EQ-5D Instrument was used in this study to estimate the utilities associated with EQ-5D
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33 195 health status [27]. Japan was the first Asian country to develop its own preference EQ-5D
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35 196 weights in 2002. The model was chosen to represent Asian preference weights [28]. VAS scores
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37 197 and utility values were reported using the mean and standard deviation (SD) of the VAS score.
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39 198 VAS scores ranged from 0 (worst HRQoL) to 100 (best HRQoL), and utility values from 0
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41 199 (death) to 1 (perfect health).
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45 200 Scores obtained for male and female patients were compared according to GW diagnosis
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47 201 (in men) and HPV-related disease or GW diagnosis (in female patients). For continuous
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49 202 variables, comparisons were performed using the student t-test or Mann-Whitney U test. In
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51 203 addition, the effect size (mean difference between the two means divided by the *pooled* standard
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53 204 deviation) between groups has been calculated. For categorical variables, differences between
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4 205 the groups were analyzed using the Chi-square or Fisher Exact test depending on patient
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7 206 distribution across response categories.

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9 207 CECA scores were reported using the mean, SD, and 95% confidence interval (CI).
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11 208 Student t-tests were performed to compare CECA scores according to gender.

14 209 **Results**

16 210 *Socio-demographic and Clinical Characteristics*

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20 211 A total of 400 patients participated in the study. Table 1 shows age, marital status, race,
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22 212 highest educational degree, and sexual activity according to gender and HPV diagnosis status.
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24 213 Approximately half of patients included in the study were age 30-44 years (45.3%), 85.9% were
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26 214 in a committed relationship, 51.6% were married, 2.3% earned an education lower than grade 12
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28 215 (including vocational studies), 75.7% were employed, and 22.5% had no health insurance or
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31 216 other health care coverage.
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218 **Table 1. Socio-demographic Characteristics and Sexual Activity of Survey Participants in**
 219 **South Korea by Gender and GW Diagnosis (men) or HPV-related Diseases (women)**

	Men (n=150)		P-value	Women (n=250)		P-value	Overall
	With GW (n=75)	No GW (n=75)		HPV Disease (n=200)	No HPV Disease (n=50)		
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)		P-value	Women (n=250)		P-value	Overall
	With GW (n=75)	No GW (n=75)		HPV Disease (n=200)	No HPV Disease (n=50)		
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

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

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4 223 The sexual activity of surveyed patients according to gender and GW or selected HPV-
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7 224 related disease is shown in Table 1. Male GW patients reported a younger age at first intercourse
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9 225 compared to female patients (20.6 [4.0] vs. 21.9 [4.2]), and had a greater number of sexual
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11 226 partners (p=0.0014) than those without GW. A higher percentage of female patients with HPV-
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13 227 related diseases reported having had sexual intercourse compared to those without HPV-related
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15 228 diseases (99.0% vs. 92.0%, p=0.0038). No statistically significant differences were observed for
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18 229 any of the remaining sexual activity questions, as reported in Table 1.
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233 *Psychosocial Impact*

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

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

	Men (n=150)		ES	P-value	Women (n=250)*		ES	P-value
	With GW (n=75)	No GW (n=75)			HPV Disease (n=200)	No HPV Disease (n=50)		
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)		ES	P-value	Women (n=250)*		ES	P-value
	With GW (n=75)	No GW (n=75)			HPV Disease (n=200)	No HPV Disease (n=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

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4 251 with selected HPV-related diseases vs. 66.0% without reported a moderate or heavy
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7 252 psychological impact [$p=0.0004$]).

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9 253 HIP scores by specific HPV-related disease were also conducted. In all domains except
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11 254 for ‘control-life impact’ and ‘emotional impact’, significant differences were identified. Higher
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13 255 scores, and thereby higher psychological impact, were reported by patients with external GW.
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15 256 All GW patients had either moderate or heavy psychological impact (90.0% and 10.0%,
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17 257 respectively). In all domains, female patients with selected HPV-related diseases had higher
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19 258 scores, reflecting a higher psychological impact (Appendix Table A-3).

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23 259 CECA scores stratified by gender are shown in Figure 1. Women with GW reported
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25 260 significantly lower scores on the ‘emotional health’ (mean [SD], 7.2 [4.2]), and ‘sexual activity’
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27 261 dimensions (11.0 [5.8]) compared to men with GW – ‘emotional health’ dimension (10.5 [3.8])
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29 262 and ‘sexual activity’ dimension (15.9 [6.1]) – indicating worse HRQoL among women.

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32 263 No significant differences were observed for problems reported by male patients in the
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34 264 EQ-5D descriptive system by GW diagnosis, as most male patients reported no problems.
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36 265 Among those who reported problems, the most frequent were ‘pain-discomfort’ (10.7%) and
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38 266 ‘anxiety-depression’ (12.7%, Table 3). Female patients with selected HPV-related diseases
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40 267 reported more problems related to the EQ-5D ‘anxiety-depression’ dimension than those without.
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42 268 Thirty-one percent of those with selected HPV-related diseases reported feeling moderately or
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44 269 extremely anxious or depressed, compared to 10.0% of female patients without HPV-related
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46 270 diseases. There were no statistically significant differences in the remaining EQ-5D items
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48 271 between female patients with and without HPV-related diseases (Table 3).
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272 **Table 3. EQ-5D Descriptive System Results by Male and Female patients with and without**
 273 **GW and Selected HPV-related Diseases in South Korea**

	Men (n=150)		P-value	Women (n=250)		P-value
	With GW (n=75)	No GW (n=75)		HPV Disease (n=200)	No HPV Disease (n=50)	
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	

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

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

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

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

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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 Table A-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)		ES	P-value	Overall	Women (n=250)		ES	P-value	Overall
	With GW (n=75)	No GW (n=75)				HPV disease (n=200)	No HPV disease (n=50)			
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; 1.0)			(0.9; 1.0)	(0.9; 0.9)	(0.9; 1.0)			(0.9; 0.9)
Valid n	75	75			150	199	50			249

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

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

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

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

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302 Female patients with selected HPV-related diseases showed numerically lower mean
303 VAS scores (72.2) and utility values (0.90) than those without selected HPV-related diseases
304 (76.86 and 0.94, respectively), but the differences were not significant. When comparing selected
305 HPV-related diseases, the lowest VAS and utility scores (worst HRQoL) were observed in GW
306 patients ($p < 0.0001$, Appendix Table A-5).

307 Discussion

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

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

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4 320 VAS scores ranged from 0 (worst imaginable health status) to 100 (best imaginable health
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7 321 status), and female patients reported worse health status (73.14) compared to male patients
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9 322 (78.16), particularly female patients with HPV-related diseases (72.18). In addition, GW patients
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11 323 reported worse HRQoL scores compared to those without GW in the disease-specific HIP
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13 324 questionnaire. Furthermore, women reported poorer health status following a GW diagnosis than
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15 325 a CIN diagnosis. These results are consistent with a Chinese study by Wang *et al* [29] which
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17 326 reported that female GW patients had the highest mean HIP scores (52.2), showing a significant
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19 327 psychological impact, followed by patients with precancerous cervical lesions (48.6), HPV after
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21 328 abnormal Pap test results (45.8), abnormal Pap test results without HPV test (44.1), and HPV
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23 329 after abnormal Pap test results (43.1).

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27 330 In the current study, HRQoL results suggest that GW in males and HPV-related disease
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29 331 (high-grade dysplasia requiring ablation treatment) in female patients had a negative impact on
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31 332 patient well-being and HRQoL scores. This study also observed that female GW patients
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33 333 suffered a major impact compared to those with other selected HPV-related diseases. Previous
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35 334 studies have shown that patients with GW had significantly lower quality of life, and substantial
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37 335 psychosocial burden with higher social stigma – especially when GW infection is symptomatic,
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39 336 visible to the naked eye, and found in the genital region [30,31,32]. In addition, a study that
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41 337 compared GW patients with asymptomatic genitourinary internal medicine patients observed that
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43 338 patients with GW had a significantly higher psychological burden because of the GW infection
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45 339 compared to the other patients. The study also observed that infection with GW not only
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47 340 influences the patient's physical wellbeing but also has a potentially detrimental effect on the
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49 341 patient's emotions [33].

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53 342 This could explain the observed poorer health status in GW patients evaluated in this study.
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4 343 Furthermore, the highest score was in the ‘partner issue and transmission’ category, followed by
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7 344 ‘worries and concerns’ and ‘emotional impact’, with a HIP mean score >60. The lowest scores
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9 345 were in the ‘control-life impact’ category (mean HIP score 45.20). A similar study using the HIP
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11 346 survey instrument in Australia found that the largest impact of GW on quality of life was in the
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13 347 domains of ‘sexual impact’, ‘self-image,’ and ‘partner and transmission’ [24].
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16 348 Based on EQ-5D survey results, GW and selected HPV-related disease patients reported
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18 349 more problems related to ‘anxiety-depression’ than those without these conditions. The current
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20 350 study detected a lower impact of GW as assessed by EQ-5D than in the previous Canadian study
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22 351 [34]. HRQoL scores in each of the questionnaires reported by female study patients were
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24 352 descriptively compared among the study subgroups (abnormal Pap result, abnormal Pap and
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26 353 HPV positive results, precancerous lesions, and external GW). While GW has an impact on
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28 354 HRQoL in the current study, the precise impact is difficult to assess due to scarcity of data and
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30 355 the heterogeneity of the instruments used to compare scores of GW patients with those of the
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32 356 general population [35].
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36 357 Shin *et al.* conducted a similar study in mainland China in 2012 and found that 56.4% of
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38 358 patients reported some problems in the ‘anxiety and depression’ dimension (highest), followed
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40 359 by ‘pain and discomfort’ (24.7%) and ‘mobility’ (3.5%) [16]. In a study from the United
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42 360 Kingdom in 2008, Woodhall *et al.* found that female GW patients had lower VAS and EQ-5D
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44 361 index scores than control patients, even after adjusting for age and gender. The difference was
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46 362 particularly notable in young women [36]. Consistent with the current study results, Woodhall *et*
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48 363 *al.* also reported that the ‘pain and discomfort’ and ‘depression and anxiety’ dimensions were the
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50 364 two most affected domains.
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4 365 This study also observed that 60% of women with no GW reported a moderate impact in
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7 366 the HIP scoring. Reasons for this impact level among these patients were not evaluated.
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9 367 However, there is the possibility that these patients may have had other conditions during
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11 368 presentation at the clinic that may have impacted their HIP score.

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13 369 Overall, the results of the current study suggest that a GW diagnosis has a great
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16 370 psychosocial impact on female patients. Other studies have provided evidence that the
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18 371 psychosocial impact of sexually transmitted disease diagnoses may be greater for women than
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20 372 for men. The origin of these differences is not clear, but they may be due to sexual infectivity
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22 373 and reproductive health [36]. Furthermore, research among women who received abnormal
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24 374 cervical smear test results have indicated that they often experienced psychosocial consequences
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26 375 including anxiety, fears about cancer, sexual difficulties, changes in body image and concerns
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28 376 regarding loss of reproductive function [13,37]. Shi *et al.* also indicated in their study that
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30 377 culture plays an important role, as conservative cultures (such as South Korea) view a diagnosis
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32 378 of a sexually transmitted disease such as GW as disgraceful. Consequently, patients would not
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34 379 seek support, even from their own families [16]. Additionally, continued study of HPV natural
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36 380 history among men from different geographic regions is necessary to elucidate the underlying
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38 381 HPV-related diseases occurring in these populations.

382 **Limitations**

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

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4 387 who sought professional GW treatment were included in the study, which may not be
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7 388 generalizable to the entire South Korean GW population. As the study was cross-sectional in
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9 389 design, it can only report the impact of GW on the patients at the time the survey was taken,
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11 390 rather than longer-term impact. However, in a longitudinal study conducted to determine the
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13 391 impact of HPV status on quality of life (QoL) in oral cavity and oropharyngeal squamous cell
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15 392 carcinoma, results showed that QoL scores were lower in HPV positive patients. [38] The study
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17 393 design is a simple descriptive comparison of outcomes, so potential factors that might mediate or
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19 394 moderate the psychosocial effects of GW were not evaluated. We recommend that for future
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21 395 studies on GW in South Korea, multivariate analysis be carried out to address these factors.
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25 396 **Conclusion**

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27 398 The diagnosis of GW, a common sexually transmitted disease, has significant associated
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29 399 morbidity – largely due to the psychosocial impact GW have on patients. Prevention of all HPV-
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31 400 related diseases, cancers, and non-cancerous lesions is important. Vaccines that have broad
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33 401 protection against multiple HPV types should be considered. In addition, the results of this study
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35 402 can help direct guidelines for patient counseling and health education and emphasize the need to
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37 403 include HPV vaccine programs as a part of national vaccine programs. The purpose of this study
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39 404 was to determine the psychosocial impact of GW among male and female patients in South
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41 405 Korea utilizing various validated tools, given that literature related to the psychosocial impact of
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43 406 GW is scarce in this country. The current study results, utilizing HRQoL, suggest that GW in
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45 407 males and high-grade dysplasia requiring ablation treatment in female patients have a negative
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47 408 impact on patient well-being and HRQoL. The psychosocial burden was particularly greater
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49 409 among female GW patients compared to those with other selected HPV-related disease.
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4 410 Although recent studies have looked at the psychosocial impact of GW on HRQoL in
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7 411 other places like China, [11] Singapore, [12] and the UK, [13] this study highlights the
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9 412 psychosocial impact of GW on HRQoL for infected patients in South Korea. Previously
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11 413 published studies used for comparison to the results of this study vary substantially in
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13 414 methodology and are different in nature due to the dissimilarities of GW across regions and
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15 415 cultures. However, the current study offers baseline data, and further research is encouraged to
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17 416 measure the psychosocial burden of GW in South Korea. Despite its limitations, the current
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19 417 study offers groundwork for measurement of the psychosocial impact of GW in South Korea that
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21 418 was previously unavailable.
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25 419 **Contributorship Statement**

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29 420 TSL, SKT, PKS, KY, AK, ARG, SMG, WJ, NL, and MR conceived and designed the experiments for
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31 421 this manuscript.
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34 422 NL, MR, SKT, PKS, AK performed the experiments for this manuscript.
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36 423 NL, MR analyzed the data for this manuscript.
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39 424 NL, MR contributed reagents/materials/analysis tools for this manuscript.
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41 425 All authors contributed to the writing of this manuscript.
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428 This study was funded by Merck and Co.

429 **Competing Interests**

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

448 **Data Sharing Agreement**

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

451 **Supporting Information**

452 **Figure Legends**

453 **Figure 1. CECA Questionnaire Scores by Male and Female Patients with GW in South** 454 **Korea**

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

457 **Participating Physicians by Region in South Korea**

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

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

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

461 **Table A-3. HIP Questionnaire Scores by Female Patients and selected HPV-related** 462 **diseases in South Korea**

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

465 **Table A-4. EQ-5D Descriptive System Results by Female Patients and selected HPV-** 466 **related Diseases in South Korea (excluding control group)**

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

468 **Table A-5. EQ-5D VAS and Utility Scores for Female Patients by selected HPV-related** 469 **Diseases in South Korea (excluding control group)**

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

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

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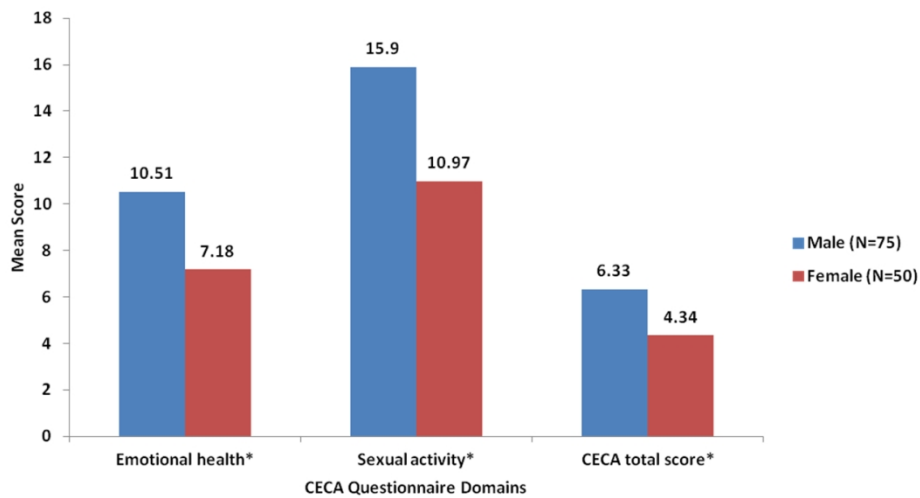


Figure 1. CECA Questionnaire Scores by Male and Female Patients with GW in South Korea / CECA=Cuestionario Específico para Condiloma Acuminado (in Spanish) – ‘Specific questionnaire for Condylomata Acuminata’; GW=genital warts

364x193mm (96 x 96 DPI)

1 APPENDIX

2 **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

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

6 **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%

8 **Table A-3. HIP Questionnaire Scores by Female Patients and selected HPV-related**
 9 **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

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11 HPV=human papillomavirus; HIP=HPV impact profile; Pap=Papanicolaou test; GW=genital warts; CI=confidence
12 interval
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15 **Table A-4. EQ-5D Descriptive System Results by Female Patients and selected HPV-related Diseases in South Korea**
 16 **(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	

17 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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up – N/A <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants – Pgs. 7-11 (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed – N/A <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed – N/A <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed – N/A <i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) – N/A
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time – N/A <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure – N/A <i>Cross-sectional study</i> —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
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*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

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Primary Subject Heading:	Sexual health
Secondary Subject Heading:	Dermatology, Sexual health, Urology, Epidemiology
Keywords:	genital warts, psychosocial impact, South Korea

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

3 **Short Title:** GW: Psychosocial Impact in South Korea

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14 **Keywords:** Genital Warts, Psychosocial impact, South Korea

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18 Abstract

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

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

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

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

31 **Results:** Of 150 male and 250 female patients, HIP scores showed 85.3% of male patients with
32 genital warts (GW) and 32.0% without reported moderate psychological impact ($p<0.0001$). In
33 categorized total scores, 88.5% of female patients with and 66.0% without selected HPV-related
34 diseases reported moderate or high psychological impacts ($p=0.0004$). In the CECA questionnaire,
35 male patients had mean (standard deviation) scores of 10.51 (3.79) in ‘emotional health’, and 15.90
36 (6.13) in ‘sexual activity’. Female patients with GW reported lower scores in both dimensions
37 with mean scores of 7.18 (4.17) in ‘emotional health’ and 10.97 (5.80) in ‘sexual activity’
38 ($p<0.0001$), indicating worse health-related quality of life (HRQOL). For the EQ-5D, male

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4 39 patients with GW reported lower mean visual analog scale scores than those without (75.1 vs.
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6 81.13, $p < 0.0135$). Mean VAS score and utility values were lower for females with HPV-related
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8 40 diseases than those without (72.18 vs. 76.86 and 0.90 vs. 0.94, respectively).
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11 42 **Conclusion:** In South Korea, GW in men and HPV-related diseases in women negatively impact
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13 43 patient well-being and HRQOL scores. Among women, those with GW suffered a greater
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15 44 psychosocial impact than those with other selected HPV-related diseases.
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19 45 **Keywords:** genital warts, psychosocial impact, South Korea
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22 46 **Article Summary:**
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25 47 **Strengths and limitations of this study**
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27

- 28 48 • Cross-sectional HIP, CECA, and EQ-5D surveys completed by patients were logged by
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30 49 multiple physician specialties and in different geographic regions in South Korea.
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33 50 • Patients were stratified into male and female groups and further stratified by GW or HPV-
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35 51 related disease status (with/without)
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38 52 • Patient survey results were used to assess psychosocial burden (general health, sexual
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40 53 activity, cervical cancer screening behavior, psychosocial impact, GW experience, socio-
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42 54 demographic information).
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46 55 • Selection bias may have occurred due to the convenience sample approach used.
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56 Introduction

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

65 To date, few studies have focused on HPV prevalence and related disease among men and
66 women residing in South Korea. The study, conducted among South Korean women, observed a
67 low-risk HPV prevalence of 10.3% among those ages 20-29 years and 3.2% among women ages
68 50-59 years [9]. While another study observed an overall GW prevalence in South Korea of 0.7%
69 [10].

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

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4 78 Recognizing the profound impact that GW and other HPV-related diseases can have on
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7 79 patients has led to the creation of tools to assess the burden of these conditions, including the self-
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9 80 administered HPV Impact Profile (HIP) as developed and validated by Mast *et al.*, the European
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11 81 quality of life (EurQol)-5 dimension (EQ-5D), and the *Cuestionario Especifico para Condiloma*
12
13 82 *Acuminado* (CECA; in Spanish) – ‘Specific questionnaire for Condylomata Acuminata’. These are
14
15 83 standardized and commonly used instruments to measure health-related quality of life (HRQoL).
16
17 84 [16,17,18]. The HIP was used in a study of Taiwanese women, and results showed that an
18
19 85 abnormal Papanicolaou (Pap) result (including abnormal results and any grade of cervical cancer)
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21 86 has a significant psychosocial impact, and a greater impact for those diagnosed with GW [19].
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23 87 Pirota *et al.* also found a significant psychosocial impact on Australian women screened for and
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25 88 diagnosed with an HPV-related disease [20]. These women were found to be more likely to have
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27 89 their social lives disrupted, even more so than those being treated for high-grade cervical dysplasia
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29 90 [20].
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34 91 Literature on the psychosocial impact of GW in South Korea is scarce. Most available
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36 92 research in the country focuses on cervical cancer, HPV knowledge and attitudes, or intention
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38 93 toward HPV vaccination [21,22,23]. The aim of this study was to evaluate the psychosocial burden
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40 94 of HPV-related diseases, including GW, in South Korea among male and female patients ages 20-
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42 95 60 years.
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97 **Materials and Methods**

98 *Study Design*

99 A cross-sectional study was conducted from July 28, 2011 to November 30, 2011 in five
100 major cities of South Korea: Seoul, Busan, Daegu, Kwangju, and Daejeon (Appendix Table A-1).
101 The study targeted clinics where cervical cytology screenings, including GW screenings, were
102 performed, and where men and women were seen for HPV-related diseases. The study was
103 approved by the National Evidence-based Health Care Collaborating Agency (NECA), Borame
104 University Hospital, the SMG-SNU University Medical Center, and the Ewha University
105 Mokdong Hospital ethics committees. No confidential patient-level data was collected for this
106 study.

107 *Inclusion and Exclusion Criteria*

108 Participating Physicians

109 Participating physicians were identified through an Intercontinental Marketing Services
110 (IMS) database, a database of nationwide clinics published by Health Insurance Review and
111 Assessment (HIRA). This database includes information pertaining to 5,098 clinics in the five
112 targeted cities (Appendix Table A-2). All data collection for this study was conducted in the office
113 or clinic of the participating physicians.

114 Patient and Public Involvement

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

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4 117 patient informed consent form with a short description of the survey. The physician provided
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6 118 verification on the survey regarding to which group the patient belonged (GW or control group)
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9 119 and administered the survey in the physician's office. Once the survey was completed, the patient's
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11 120 survey was placed in a sealed envelope and left at the physician's office to be sent or picked up by
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13 121 a research coordinator. Patients were not involved in the recruitment to and conduct of the study.
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16 122 Physicians were asked to read the corresponding questions to the patients to avoid any
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18 123 misinterpretation of questions. The results will not be disseminated to study participants. The
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20 124 current study was not a randomized controlled trial.
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23 24 125 Female Patients

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27 126 Female patients were included in the study if they were between the ages of 20 and 60
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29 127 years, experienced an HPV-related event within the past 3 months, were in good self-reported
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31 128 health, and belonged to one of the following categories: a) Abnormal Pap test result with no
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33 129 definitive histology, conforming to the Bethesda Category-2001 category of squamous or
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35 130 glandular cell abnormality (for example: atypical cells of undetermined significance [ASCUS],
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37 131 atypical glandular cells of undetermined significance [AGUS], low-grade squamous intraepithelial
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39 132 lesion [LSIL] or high-grade squamous intraepithelial lesion [HSIL]) and no previous high-risk
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41 133 HPV test performed; b) receipt of positive high-risk HPV DNA test results after an abnormal Pap
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43 134 test, as defined in the previous category; c) diagnosis of external GW or treatment for recurrences;
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45 135 d) histological diagnosis of HPV-related cervical dysplasia cervical lesion (eg, CIN1, CIN2, CIN
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48 136 3); e) normal Pap result with no abnormal Pap test or definitive therapy within the past year; or f)
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51 137 two or more of the above conditions (not including GW patients) were categorized in the upper
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54 138 level of disease. To enable categorizing of women into discreet disease groups of CIN versus GW,
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4 139 female patients were excluded from the study if they were diagnosed with GW and had any of the
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7 140 following: precancerous cervical lesions, abnormal Pap and HPV-positive, or abnormal Pap test
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9 141 results.

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12 142 The control group was selected from the same clinic as the case group. Physicians provided
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14 143 verification on the survey regarding patient groups (GW or control group) and gave them the
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16 144 survey to complete in the physician's office. The physician sample was divided across primary
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18 145 care physicians (general practitioners and internal medicine), obstetrics/gynecologists, urologists,
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20 146 and dermatologists. The control group consisted of patients who have never had GW or received
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22 147 treatment for it or had surgery or therapy in the genital area and included all other patients from a
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24 148 physician's practice or clinic.

25 26 27 28 29 149 Male Patients

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32 150 Male patients were included in the study if they were between ages 20 and 60 years, in
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34 151 good self-reported physical health, and belonged to one of the following categories: a) newly
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36 152 diagnosed or existing external GW within the past 3 months of study recruitment; and b) patients
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38 153 who had never been diagnosed with GW, prescribed GW treatment or had surgery or therapy in
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40 154 the genital area.

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43 155 Male and female patients were excluded from the study if they: a) had presence of any
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45 156 other concurrent/active STI; b) were concurrently enrolled in clinical studies of investigational
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47 157 agents; c) had a history of known prior or recent (within 1 year of the enrollment date) HPV
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49 158 vaccination; d) had ongoing alcohol or drug abuse; e) were unable to give informed consent; or f)
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51 159 had presence of any condition, which in the opinion of the investigator could interfere with the
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53 160 evaluation of the study objectives.

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4 161 *Survey Instruments*
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7 162 To measure the psychosocial burden (general health, sexual activity, cervical cancer
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9 163 screening behavior, psychosocial impact, GW experience, socio-demographic information),
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11 164 participants completed the three validated questionnaires; HIP (HPV Impact Profile), CECA
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13 165 (*Cuestionario Especifico para Condiloma Acuminado* in Spanish– ‘Specific questionnaire for
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15 166 Condylomata Acuminata’) and EQ-5D (EuroQol-5 Dimension) surveys, which were translated to
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17 167 the Korean language and culturally pre-tested. Questionnaires were administered by the
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19 168 participating physician after patients were diagnosed with HPV-related disease. A pilot test was
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21 169 conducted using a small sample of physicians representing all four types of study physicians (two
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23 170 per specialty, eight total). This was to ensure that all survey questions and exercises were
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25 171 understood by respondents, and included culturally appropriate information.
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30 172 HIP is a validated, 29-item self-administered questionnaire, designed to measure the
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32 173 psychosocial impact of HPV-related health conditions in women [15]. The response for each item
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34 174 ranges from 0 (lowest impact) to 10 points (highest impact). Items in the HIP survey were linearly
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36 175 transformed to a 0-100 scale, with higher scores indicating better health. To create scale scores,
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38 176 the mean was computed as the sum of the item scores over the number of items answered to
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40 177 account for missing data. If more than 50% of items on the scale were missing, the score was not
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42 178 computed. To create the total scale score, the mean was computed as the sum of all items over the
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44 179 number of items answered on all scales [24]. The scale uses visual-spatial, numeric, and verbal
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46 180 descriptive anchors to assess subject responses. This survey was adapted for use in male patients
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48 181 in consultation with the original developer and has undergone cognitive testing in the United
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50 182 States. Overall HIP scores are categorized as: no or little impact (mean HIP score <40), moderate
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52 183 impact (between 40 and 70) and heavy psychological impact (mean HIP score >70) [19].
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4 184 The CECA survey includes 10 questions across two domains: emotional and sexual activity
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6 185 [18,25]. CECA scores range from 0 (worst HRQoL) to 100 (best HRQoL). The EQ-5D survey is
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9 186 a two-part questionnaire, including descriptive and thermometer or visual analog scale (VAS), and
10
11 187 serves as a generic validated instrument for use as a measure of HRQoL [26]. VAS scores range
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13 188 from 0 (death) to 100 (perfect health).

16 189 *Statistical Analysis*

19 190 All study outcomes were summarized descriptively. A descriptive analysis of the EQ-5D
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21
22 191 questionnaire was performed and numbers and percentages were provided. The Japanese version
23
24 192 of the EQ-5D Instrument was used in this study to estimate the utilities associated with EQ-5D
25
26 193 health status [27]. Japan was the first Asian country to develop its own preference EQ-5D weights
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28 194 in 2002. The model was chosen to represent Asian preference weights [28]. VAS scores and utility
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30 195 values were reported using the mean and standard deviation (SD) of the VAS score. VAS scores
31
32 196 ranged from 0 (worst HRQoL) to 100 (best HRQoL), and utility values from 0 (death) to 1 (perfect
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34 197 health).

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36 198 Scores obtained for male and female patients were compared according to GW diagnosis
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38 199 (in men) and HPV-related disease or GW diagnosis (in female patients). For continuous variables,
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41 200 comparisons were performed using the student t-test or Mann-Whitney U test. In addition, the
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43 201 effect size (mean difference between the two means divided by the *pooled* standard deviation)
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45 202 between groups has been calculated. For categorical variables, differences between the groups
46
47 203 were analyzed using the Chi-square or Fisher Exact test depending on patient distribution across
48
49 204 response categories.

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

207 **Results**

208 *Socio-demographic and Clinical Characteristics*

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

215

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

	Men (n=150)		P-value	Women (n=250)		P-value	Overall
	With GW (n=75)	No GW (n=75)		HPV Disease (n=200)	No HPV Disease (n=50)		
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)		P-value	Women (n=250)		P-value	Overall
	With GW (n=75)	No GW (n=75)		HPV Disease (n=200)	No HPV Disease (n=50)		
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

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219

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

221 The sexual activity of surveyed patients according to gender and GW or selected HPV-
222 related disease is shown in Table 1. Male GW patients reported a younger age at first intercourse
223 compared to female patients (20.6 [4.0] vs. 21.9 [4.2]), and had a greater number of sexual partners
224 (p=0.0014) than those without GW. A higher percentage of female patients with HPV-related
225 diseases reported having had sexual intercourse compared to those without HPV-related diseases
226 (99.0% vs. 92.0%, p=0.0038). No statistically significant differences were observed for any of the
227 remaining sexual activity questions, as reported in Table 1.

228

229

231 *Psychosocial Impact*

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

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

	Men (n=150)		ES	P-value	Women (n=250)*		ES	P-value
	With GW (n=75)	No GW (n=75)			HPV Disease (n=200)	No HPV Disease (n=50)		
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)		ES	P-value	Women (n=250)*		ES	P-value
	With GW (n=75)	No GW (n=75)			HPV Disease (n=200)	No HPV Disease (n=50)		
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

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4 248 disease had higher scores, reflecting a higher psychological impact (88.5% of female patients with
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6 249 selected HPV-related diseases vs. 66.0% without reported a moderate or heavy psychological
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9 250 impact [$p=0.0004$]).

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11 251 HIP scores by specific HPV-related disease were also conducted. In all domains except for
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13 252 ‘control-life impact’ and ‘emotional impact’, significant differences were identified. Higher scores,
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15 253 and thereby higher psychological impact, were reported by patients with external GW. All GW
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17 254 patients had either moderate or heavy psychological impact (90.0% and 10.0%, respectively). In
18
19 255 all domains, female patients with selected HPV-related diseases had higher scores, reflecting a
20
21 256 higher psychological impact (Appendix Table A-3).

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25 257 CECA scores stratified by gender are shown in Figure 1. Women with GW reported
26
27 258 significantly lower scores on the ‘emotional health’ (mean [SD], 7.2 [4.2]), and ‘sexual activity’
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29 259 dimensions (11.0 [5.8]) compared to men with GW – ‘emotional health’ dimension (10.5 [3.8])
30
31 260 and ‘sexual activity’ dimension (15.9 [6.1]) – indicating worse HRQoL among women.

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34 261 No significant differences were observed for problems reported by male patients in the EQ-
35
36 262 5D descriptive system by GW diagnosis, as most male patients reported no problems. Among
37
38 263 those who reported problems, the most frequent were ‘pain-discomfort’ (10.7%) and ‘anxiety-
39
40 264 depression’ (12.7%, Table 3). Female patients with selected HPV-related diseases reported more
41
42 265 problems related to the EQ-5D ‘anxiety-depression’ dimension than those without. Thirty-one
43
44 266 percent of those with selected HPV-related diseases reported feeling moderately or extremely
45
46 267 anxious or depressed, compared to 10.0% of female patients without HPV-related diseases. There
47
48 268 were no statistically significant differences in the remaining EQ-5D items between female patients
49
50 269 with and without HPV-related diseases (Table 3).

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

	Men (n=150)		P-value	Women (n=250)		P-value
	With GW (n=75)	No GW (n=75)		HPV Disease (n=200)	No HPV Disease (n=50)	
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	

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

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

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

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

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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 Table A-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)		ES	P-value	Overall	Women (n=250)		ES	P-value	Overall
	With GW (n=75)	No GW (n=75)				HPV disease (n=200)	No HPV disease (n=50)			
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; 1.0)			(0.9; 1.0)	(0.9; 0.9)	(0.9; 1.0)			(0.9; 0.9)
Valid n	75	75			150	199	50			249

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

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

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

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

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300 Female patients with selected HPV-related diseases showed numerically lower mean VAS
301 scores (72.2) and utility values (0.90) than those without selected HPV-related diseases (76.86 and
302 0.94, respectively), but the differences were not significant. When comparing selected HPV-
303 related diseases, the lowest VAS and utility scores (worst HRQoL) were observed in GW patients
304 ($p < 0.0001$, Appendix Table A-5).

305 Discussion

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

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

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4 318 ranged from 0 (worst imaginable health status) to 100 (best imaginable health status), and female
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7 319 patients reported worse health status (73.14) compared to male patients (78.16), particularly female
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9 320 patients with HPV-related diseases (72.18). In addition, GW patients reported worse HRQoL
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11 321 scores compared to those without GW in the disease-specific HIP questionnaire. Furthermore,
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13 322 women reported poorer health status following a GW diagnosis than a CIN diagnosis. These results
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15
16 323 are consistent with a Chinese study by Wang *et al* [29] which reported that female GW patients
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18 324 had the highest mean HIP scores (52.2), showing a significant psychological impact, followed by
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21 325 patients with precancerous cervical lesions (48.6), HPV after abnormal Pap test results (45.8),
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23 326 abnormal Pap test results without HPV test (44.1), and HPV after abnormal Pap test results (43.1).

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25 327 In the current study, HRQoL results suggest that GW in males and HPV-related disease
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27 328 (high-grade dysplasia requiring ablation treatment) in female patients had a negative impact on
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30 329 patient well-being and HRQoL scores. This study also observed that female GW patients suffered
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32 330 a major impact compared to those with other selected HPV-related diseases. Previous studies have
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34 331 shown that patients with GW had significantly lower quality of life, and substantial psychosocial
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37 332 burden with higher social stigma – especially when GW infection is symptomatic, visible to the
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39 333 naked eye, and found in the genital region [30,31,32]. In addition, a study that compared GW
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41 334 patients with asymptomatic genitourinary internal medicine patients observed that patients with
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44 335 GW had a significantly higher psychological burden because of the GW infection compared to the
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46 336 other patients. The study also observed that infection with GW not only influences the patient's
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48 337 physical wellbeing but also has a potentially detrimental effect on the patient's emotions [33].
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50 338 This could explain the observed poorer health status in GW patients evaluated in this study.
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53 339 Furthermore, the highest score was in the 'partner issue and transmission' category, followed by
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55 340 'worries and concerns' and 'emotional impact', with a HIP mean score >60. The lowest scores

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4 341 were in the ‘control-life impact’ category (mean HIP score 45.20). A similar study using the HIP
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6 342 survey instrument in Australia found that the largest impact of GW on quality of life was in the
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9 343 domains of ‘sexual impact’, ‘self-image,’ and ‘partner and transmission’ [24].
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11 344 Based on EQ-5D survey results, GW and selected HPV-related disease patients reported
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13 345 more problems related to ‘anxiety-depression’ than those without these conditions. The current
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16 346 study detected a lower impact of GW as assessed by EQ-5D than in the previous Canadian study
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18 347 [34]. HRQoL scores in each of the questionnaires reported by female study patients were
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20 348 descriptively compared among the study subgroups (abnormal Pap result, abnormal Pap and HPV
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22 349 positive results, precancerous lesions, and external GW). While GW has an impact on HRQoL in
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25 350 the current study, the precise impact is difficult to assess due to scarcity of data and the
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27 351 heterogeneity of the instruments used to compare scores of GW patients with those of the general
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30 352 population [35].
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32 353 Shin *et al.* conducted a similar study in mainland China in 2012 and found that 56.4% of
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34 354 patients reported some problems in the ‘anxiety and depression’ dimension (highest), followed by
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36 355 ‘pain and discomfort’ (24.7%) and ‘mobility’ (3.5%) [16]. In a study from the United Kingdom in
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39 356 2008, Woodhall *et al.* found that female GW patients had lower VAS and EQ-5D index scores
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41 357 than control patients, even after adjusting for age and gender. The difference was particularly
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43 358 notable in young women [36]. Consistent with the current study results, Woodhall *et al.* also
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46 359 reported that the ‘pain and discomfort’ and ‘depression and anxiety’ dimensions were the two most
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48 360 affected domains.
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50 361 This study also observed that 60% of women with no GW reported a moderate impact in
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53 362 the HIP scoring. Reasons for this impact level among these patients were not evaluated. However,
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4 363 there is the possibility that these patients may have had other conditions during presentation at the
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7 364 clinic that may have impacted their HIP score.

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9 365 Overall, the results of the current study suggest that a GW diagnosis has a great
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11 366 psychosocial impact on female patients. Other studies have provided evidence that the
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13 367 psychosocial impact of sexually transmitted disease diagnoses may be greater for women than for
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15 368 men. The origin of these differences is not clear, but they may be due to sexual infectivity and
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17 369 reproductive health [36]. Furthermore, research among women who received abnormal cervical
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19 370 smear test results have indicated that they often experienced psychosocial consequences including
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21 371 anxiety, fears about cancer, sexual difficulties, changes in body image and concerns regarding loss
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23 372 of reproductive function [13,37]. Shi *et al.* also indicated in their study that culture plays an
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25 373 important role, as conservative cultures (such as South Korea) view a diagnosis of a sexually
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27 374 transmitted disease such as GW as disgraceful. Consequently, patients would not seek support,
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29 375 even from their own families [16]. Additionally, continued study of HPV natural history among
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31 376 men from different geographic regions is necessary to elucidate the underlying HPV-related
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33 377 diseases occurring in these populations.

38 **Limitations**

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43 379 The current study is limited, as selection bias may have occurred due to the convenience
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45 380 sample approach used. The data were collected in participating physician offices and clinics
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47 381 through questionnaires and interview-based surveys. Patients may have given expected rather than
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49 382 truthful answers, which may not give the true psychosocial impact. Moreover, only patients who
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51 383 sought professional GW treatment were included in the study, which may not be generalizable to
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53 384 the entire South Korean GW population. As the study was cross-sectional in design, it can only
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4 385 report the impact of GW on the patients at the time the survey was taken, rather than longer-term
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6 386 impact. However, in a longitudinal study conducted to determine the impact of HPV status on
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8 387 quality of life (QoL) in oral cavity and oropharyngeal squamous cell carcinoma, results showed
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10 388 that QoL scores were lower in HPV positive patients. [38] The study design is a simple descriptive
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12 389 comparison of outcomes, so potential factors that might mediate or moderate the psychosocial
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14 390 effects of GW were not evaluated. We recommend that for future studies on GW in South Korea,
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16 391 multivariate analysis be carried out to address these factors.
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21 392 **Conclusion**

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23 394 The diagnosis of GW, a common sexually transmitted disease, has significant associated
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25 395 morbidity – largely due to the psychosocial impact GW have on patients. Prevention of all HPV-
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27 396 related diseases, cancers, and non-cancerous lesions is important. Vaccines that have broad
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29 397 protection against multiple HPV types should be considered. In addition, the results of this study
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31 398 can help direct guidelines for patient counseling and health education and emphasize the need to
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33 399 include HPV vaccine programs as a part of national vaccine programs. The purpose of this study
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35 400 was to determine the psychosocial impact of GW among male and female patients in South Korea
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37 401 utilizing various validated tools, given that literature related to the psychosocial impact of GW is
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39 402 scarce in this country. The current study results, utilizing HRQoL, suggest that GW in males and
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41 403 high-grade dysplasia requiring ablation treatment in female patients have a negative impact on
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43 404 patient well-being and HRQoL. The psychosocial burden was particularly greater among female
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45 405 GW patients compared to those with other selected HPV-related disease.
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51 406 Although recent studies have looked at the psychosocial impact of GW on HRQoL in other
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53 407 places like China, [11] Singapore, [12] and the UK, [13] this study highlights the psychosocial
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55 408 impact of GW on HRQoL for infected patients in South Korea. Previously published studies used
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4 409 for comparison to the results of this study vary substantially in methodology and are different in
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7 410 nature due to the dissimilarities of GW across regions and cultures. However, the current study
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9 411 offers baseline data, and further research is encouraged to measure the psychosocial burden of GW
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11 412 in South Korea. Despite its limitations, the current study offers groundwork for measurement of
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13 413 the psychosocial impact of GW in South Korea that was previously unavailable.
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16 414 **Contributorship Statement**

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20 415 TSL, SKT, PKS, KY, AK, ARG, SMG, WJ, NL, and MR conceived and designed the experiments for
21
22 416 this manuscript.

23
24 417 NL, MR, SKT, PKS, AK performed the experiments for this manuscript.

25
26
27 418 NL, MR analyzed the data for this manuscript.

28
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30 419 NL, MR contributed reagents/materials/analysis tools for this manuscript.

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32 420 All authors contributed to the writing of this manuscript.
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423 This study was funded by Merck and Co.

424 Competing Interests

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

443 **Data Sharing Agreement**

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

446 **Supporting Information**

447 **Figure Legends**

448 **Figure 1. CECA Questionnaire Scores by Male and Female Patients with GW in South** 449 **Korea**

450 CECA=*Cuestionario Especifico para Condiloma Acuminado* (in Spanish) – ‘Specific questionnaire for
451 Condylomata Acuminata’; GW=genital warts

452 **Participating Physicians by Region in South Korea**

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

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

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

456 **Table A-3. HIP Questionnaire Scores by Female Patients and selected HPV-related**

457 **diseases in South Korea**

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

460 **Table A-4. EQ-5D Descriptive System Results by Female Patients and selected HPV-** 461 **related Diseases in South Korea (excluding control group)**

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

463 **Table A-5. EQ-5D VAS and Utility Scores for Female Patients by selected HPV-related** 464 **Diseases in South Korea (excluding control group)**

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

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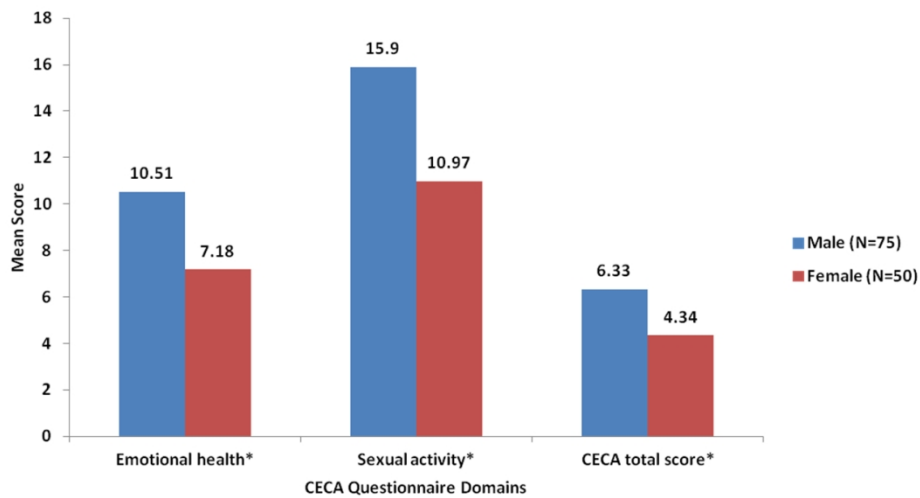


Figure 1. CECA Questionnaire Scores by Male and Female Patients with GW in South Korea / CECA=Cuestionario Específico para Condiloma Acuminado (in Spanish) – ‘Specific questionnaire for Condylomata Acuminata’; GW=genital warts

364x193mm (96 x 96 DPI)

1 APPENDIX

2 **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

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

6 **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%

8 **Table A-3. HIP Questionnaire Scores by Female Patients and selected HPV-related**
 9 **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

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15 **Table A-4. EQ-5D Descriptive System Results by Female Patients and selected HPV-related Diseases in South Korea**
 16 **(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	

17 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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up – N/A <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants – Pgs. 7-11 (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed – N/A <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed – N/A <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed – N/A <i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) – N/A
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time – N/A <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure – N/A <i>Cross-sectional study</i> —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
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*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.