

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A Cross-sectional Study Estimating the Psychosocial Impact of Genital Warts and Other Anogenital Diseases in South Korea
AUTHORS	Lee, Taek Sang; Kothari-Talwar, Smita; Singhal, Puneet; Yee, Karen; Kulkarni, Amit; Lara, Nuria; Roset, Montserrat; Giuliano, Anna; Garland, Suzanne; Ju, Woong

VERSION 1 – REVIEW

REVIEWER	Sarah Flynn University of the Cumberlands
REVIEW RETURNED	06-Sep-2017

GENERAL COMMENTS	<p>Although the topic is important, the manuscript had several limitations in both design and analyses.</p> <ol style="list-style-type: none">1. The references are almost all 5 years old or much older. There are several newer studies that describe the psychosocial impact of HPV.2. The study is a cross sectional design which limits the authors' ability to claim GW has 'significant' psychosocial impact that may last. We also are unable to tell to what degree this impact changes relative to time of diagnosis.3. The test statistics and effect sizes are not reported. It's hard to tell what test were ran on which outcome variables. Confidence intervals and p values alone are not sufficient to detect any statistical errors in analysis.4. Without effect sizes being reported, the authors' can make no claims about the degree of impact. Statistical significance does not provide this information.5. The design as a simple descriptive comparison of outcomes does not provide rich information about what factors may mediate or moderate the psychosocial effects of GW, or provide information about why gender effects may truly exist.
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REVIEWER	Caio Cavassan de Camargo Universidade do Sagrado Coração Brazil
REVIEW RETURNED	27-Sep-2017

GENERAL COMMENTS	The manuscript is pertinent for publication, but perhaps could be more enriching if the diagnosis of HPV in men did not have to restrict only the presence or absence of warts, because subclinical wart, after diagnosed cause more impairment than warts. Its also
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	necessary to update the references used since most of them have already been published for more than 5 years and there are new publication involving quality life on patients with HPV-warts
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REVIEWER	Helen Kelly London School of Hygiene and Tropical Medicine United Kingdom
REVIEW RETURNED	20-Nov-2017

GENERAL COMMENTS	<p>Estimating the Psychosocial Impact of Genital Warts in South Korea</p> <p>This cross sectional study aimed to evaluate the psychosocial impact of anogenital warts (GW) among men and women in South Korea, and reported a greater psychosocial impact of GW (and other HPV-related disease) among women compared to men. These findings are useful from the point of view of understanding the potential benefit of different HPV vaccines. However, clarifications are required on several aspects of the methods, results and interpretation.</p> <p>Title</p> <ul style="list-style-type: none"> • Given that the women included in the study also had HPV related disease, should this not be reflected in the title? <p>Abstract</p> <ul style="list-style-type: none"> • It is unclear if the participants are the primary care physicians or the 150 male and 250 female patients. I think the participants are those patients attending clinics with and without genital warts and HPV related disease? Should this be clarified ? • What are the HPV-related diseases among the females? Is it abnormal pap result? This should be clarified. • Was it possible to compare the quality of life scores between males and females (with p-value)? <p>Introduction :</p> <ul style="list-style-type: none"> • Line 7, page 5 should say "...common viral sexually transmitted infection.." <p>Methods :</p> <ul style="list-style-type: none"> • It is unclear the usefulness of the long paragraph on "Participating physicians" –they are not the participants of the study. Did they administer the questionnaire? • It is unclear how the 150 male and 250 female patients were selected. Was it at random? Consecutive? • On page 8, line 49 – it is unclear why the women with GW AND with precancerous lesions or abnormal pap were excluded as the results tables combine women who had GW only or abnormal pap/precancerous lesions (i.e. the results tables did not present data by discrete disease groups of CIN vs. GW). • How was the status of the women with HPV related disease determined? Self report? • There is no information as to how the controls (i.e. those without GW/HPV related disease) were selected. Were they recruited from the same clinics as men and women with GW? • A rationale for inclusion of all three quality of life tools is missing. Why choose all three - What is the role and interplay of each? Do some of the tools address different aspects of psychosocial stress/anxiety? Were each of them validated? • How are the different QOL systems scored? It may be useful to have an example of some of the questions asked. • Was the questionnaire administered before or after GW diagnosis? Who administered the questionnaire? <p>Results:</p> <ul style="list-style-type: none"> • Is there any reason for a higher number of women vs. men? • Line 35 on page 11 needs to be revised –not all of these factors
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are presented in Table 1.

- Could the authors report on any statistically significant difference between males and females with respect to sexual behaviour and GW diagnosis? For example, line 54 “Male GW patients reported a younger age at first sexual intercourse..” – could the authors provide a p-value? It also appears that a higher proportion of females never used condoms compare to males- could this be statistically significant? And could this have any bearing on the results?
- Table 3 : should the row titled “Women with GW” not be “Women with HPV related disease”? as per Table 1 and Table 2? The methods indicated (page 8, line 49) that women would be categorised according to whether they had discrete outcomes of GW or HPV related disease (abnormal pap smear). Would the author expect that these discrete groups of women would have similar health related quality of life scores? Would it not be justifiable to present the HIP, CECA and EQ-5D scores separately for women with GW and women with HPV related disease ?
- It would be helpful if Tables 3, 4 and 5 had footnote explaining how the scoring system is established; e.g for Table 3: HIP items range from 0 (lowest impact) to no to little impact (mean HIP score <40)...etc.
- Table 3: it is interesting that 60% of women with no GW reported moderate impact in the HIP scoring. What could explain this score in the control group (again, this argues for a better description, explanation of how the controls, i.e. women without GW/HPV related disease, were selected).
- There was a greater proportion of women with GW (or HPV related disease) who reported feeling moderately depressed compared to women without GW/HPV related disease – but the same association was not observed among men. Could this be influenced by the whether women had HPV related disease or not?
- Line 13, page 19 has an error link to Table. Similarly line 56 on same page.
- Table 1 and Table 2 could be combined in a single table.

Discussion

- Line 7, page 20 should say “This cross-sectional study estimated the psychosocial burden of GW and HPV related disease in South Korea...”
- Line 40, page 20 “women reported poorer health status following a GW diagnosis than a CIN diagnosis”, and Line 5, page 21 “Female GW patients suffered a major impact compared to those with other selected HPV-related diseases”. This appears surprising– why might this be?
- It would it be useful to discuss the implications of these findings in relation to currently available HPV vaccines and decision making on which vaccines to include in national programmes, i.e. bivalent vs. quadri/nonavalent?
- Limitations – Line 47 – could this not be an overestimate of the true effect?
- Conclusion: “this study highlights the lack of information on the psychosocial impact of GW on HRQoL” – could the authors consider other evidence available including Tan et al (Sex Health. 2014 Sep;11(4:)), Qi et al (BMC Public Health. 2014 Jul 21;14:739.), Dominiak-Felden et al (BMC Public Health. 2013 Nov 12;13:1065.)

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Sarah Flynn

Institution and Country: University of the Cumberland Please state any competing interests: None

Please leave your comments for the authors below Although the topic is important, the manuscript had several limitations in both design and analyses.

1. The references are almost all 5 years old or much older. There are several newer studies that describe the psychosocial impact of HPV.

We thank Reviewer 1 for their assessment of the manuscript. The following references have been included in the manuscript in the introduction and discussion sections:

Flores-Díaz, Ema, et al. HPV-6 molecular variants association with the development of genital warts in men: The HIM Study. *The Journal of infectious diseases*. 2016;215(4): 559-565.

Stamm AW, Kobashi KC, Stefanovic KB. Urologic Dermatology: a Review. *Current Urology Reports*. 2017;18(8):62.

Lee, Taek Sang, et al. A cross-sectional study estimating the burden of illness related to genital warts in South Korea. *BMJ open* 2017;7(6): e014217.

Tan, Lucinda S., et al. Assessment of psychosocial impact of genital warts among patients in Singapore. *Sexual health*. 2014;11(4): 313-318.

Qi, Shu-Zhen, et al. Human papillomavirus-related psychosocial impact of patients with genital warts in China: a hospital-based cross-sectional study. *BMC public health*. 2014; 14(1): 739.

Dominiak-Felden, Géraldine, et al. Impact of human papillomavirus-related genital diseases on quality of life and psychosocial wellbeing: results of an observational, health-related quality of life study in the UK. *BMC public health*. 2013: 13(1); 1065.

2. The study is a cross sectional design which limits the authors' ability to claim GW has 'significant' psychosocial impact that may last. We also are unable to tell to what degree this impact changes relative to time of diagnosis.

We agree that this study design limits the authors' ability to claim GW has 'significant' psychosocial impact that may last and to what degree this impact changes relative to time of diagnosis.

The following has been included in the discussion section of the manuscript to address this limitation “As the study was cross-sectional in design, it can only report the impact of GW on the patients at the time the survey was taken, rather than longer-term impact. However, in a longitudinal study conducted to determine the impact of HPV status on quality of life (QoL) in oral cavity and oropharyngeal squamous cell carcinoma, results showed that QoL scores were lower in HPV positive patients”. Page 22 lines 452-456

3. The test statistics and effect sizes are not reported. It's hard to tell what test were ran on which outcome variables. Confidence intervals and p values alone are not sufficient to detect any statistical errors in analysis.

The tests used for the study include the following in the methods section: “for continuous variable comparisons were performed using the student t-test or Mann-Whitney U test. For categorical variables, differences between the groups were assessed using the Chi-square or Fisher Exact test depending on patient distribution across response categories.” P-values and confidence intervals are reported. Standardized differences are not reported for any results. Page 10 lines 250-253

4. Without effect sizes being reported, the authors' can make no claims about the degree of impact. Statistical significance does not provide this information.

We agree that without effect sizes it is difficult to make claims about the degree of impact. However, with the statistical significance seen from the p-value and confidence interval in this study, we can state that there is some psychosocial impact of GW. on the patients.

5. The design as a simple descriptive comparison of outcomes does not provide rich information about what factors may mediate or moderate the psychosocial effects of GW, or provide information about why gender effects may truly exist.

This is the first full description of genital warts for the South Korean population. As such, this manuscript by necessity focuses on presenting the prevalence by sex and sub-group. A full analysis of factors mediating the outcomes requires a separate devoted analysis and manuscript that is beyond the scope of this first manuscript for South Korea.

The following has been included in the limitation section of the manuscript “The study design is a simple descriptive comparison of outcomes, so potential factors that might mediate or moderate the psychosocial effects of GW were not evaluated.” Page 22, lines 456-459

Reviewer: 2

Reviewer Name: Caio Cavassan de Camargo

Institution and Country: Universidade do Sagrado Coração, Brazil Please state any competing interests: None declared

Please leave your comments for the authors below The manuscript is pertinent for publication, but perhaps could be more enriching if the diagnosis of HPV in men did not have to restrict only the presence or absence of warts, because subclinical wart, after diagnosed cause more impairment than warts. It's also necessary to update the references used since most of them have already been published for more than 5 years and there are new publication involving quality life on patients with HPV-warts

We thank Reviewer 2 for their assessment of the manuscript. We agree with the authors that HPV detection in men is an important area of study as it pertains to significant disease in men, in addition to genital warts. However, such an evaluation requires a different study design and methods (ie, a devoted study to sampling all men for HPV and assessing genital HPV prevalence and natural history, such as was done in the HIM Study, whose findings we cite). This study was restricted to the evaluation of genital warts in a previously under-studied population of males and females in South Korea.

The following line has been added in the discussion section “Additionally, continued study of HPV natural history among men from different geographic regions is necessary to elucidate the underlying HPV-related diseases occurring in these populations” on Page 21 line 440-442

In addition, as raised by Reviewer 1, the following references have been added:

Flores-Díaz, Ema, et al. HPV-6 molecular variants association with the development of genital warts

in men: The HIM Study. *The Journal of infectious diseases*. 2016;215(4): 559-565.

Stamm AW, Kobashi KC, Stefanovic KB. *Urologic Dermatology: a Review*. *Current Urology Reports*. 2017;18(8):62.

Lee, Taek Sang, et al. A cross-sectional study estimating the burden of illness related to genital warts in South Korea. *BMJ open* 2017;7(6): e014217.

Tan, Lucinda S., et al. Assessment of psychosocial impact of genital warts among patients in Singapore. *Sexual health*. 2014;11(4): 313-318.

Qi, Shu-Zhen, et al. Human papillomavirus-related psychosocial impact of patients with genital warts in China: a hospital-based cross-sectional study. *BMC public health*. 2014; 14(1): 739.

Dominiak-Felden, Géraldine, et al. Impact of human papillomavirus-related genital diseases on quality of life and psychosocial wellbeing: results of an observational, health-related quality of life study in the UK. *BMC public health*. 2013: 13(1); 1065.

Reviewer: 3

Reviewer Name: Helen Kelly

Institution and Country: London School of Hygiene and Tropical Medicine, United Kingdom Please state any competing interests: None declared

Please leave your comments for the authors below Estimating the Psychosocial Impact of Genital Warts in South Korea

This cross-sectional study aimed to evaluate the psychosocial impact of anogenital warts (GW) among men and women in South Korea, and reported a greater psychosocial impact of GW (and other HPV-related disease) among women compared to men.

These findings are useful from the point of view of understanding the potential benefit of different HPV vaccines.

However, clarifications are required on several aspects of the methods, results, and interpretation.

Title

- Given that the women included in the study also had HPV related disease, should this not be reflected in the title?

We thank Reviewer 3 for their assessment of the manuscript. The title of the manuscript has been changed to “A Cross-sectional Study Estimating the Psychological Impact of Genital Warts and other anogenital Diseases in South Korea.”

Abstract

- It is unclear if the participants are the primary care physicians or the 150 male and 250 female patients. I think the participants are those patients attending clinics with and without genital warts and HPV related disease? Should this be clarified?

Thank you for calling our attention to the wording. It has now been changed to “Patients with and without GW (males) and selected HPV diseases (females) visiting primary care physicians (PCPs; general practice/family medicine), OB/GYNs, UROs, and dermatologists (DERMs) with 2-30 years’ experience participated in the study” Page 2, lines 32-34

- What are the HPV-related diseases among the females? Is it abnormal pap result? This should be clarified.

Females with HPV-related disease belonged to one of the following categories:

- a) Abnormal Pap test result with no definitive histology, conforming to the Bethesda Category-2001 category of squamous or glandular cell abnormality (for example: atypical cells of undetermined significance [ASCUS], atypical glandular cells of undetermined significance [AGUS], low-grade squamous intraepithelial lesion [LSIL] or high-grade squamous intraepithelial lesion [HSIL]) and no previous high-risk HPV test performed;
 - b) receipt of positive high-risk HPV DNA test results after an abnormal Pap test, as defined in the previous category;
 - c) diagnosis of external GW or treatment for recurrences;
 - d) histological diagnosis of HPV-related cervical dysplasia cervical lesion (eg, CIN1, CIN2, CIN3);
- page 7, lines 178-185

- Was it possible to compare the quality of life scores between males and females (with p-value??)

The focus of the study was to compare the characteristics and psychological impact among patients with and without GW for males and with and without HPV-related diseases for females. We did not compare the quality of life score between males and females as the diseases they experienced were different. In females we lump GW and dysplasia (pre-cancer) whereas in men it is only a non-cancerous lesion – GW that was examined. If we make a comparison then we must restrict to comparing QoL following GW only lesions in males and females. Also, Koutsky et al showed that women with different disease states have a different psychological response to GW vs dysplasia. A study in the literature (Pirota et al) found that genital warts have a significant impact on quality of life in HPV-related diseased women.

Reference:

1. Koutsky LA, Holmes KK, Critchlow CW, Stevens CE, Paavonen J, Beckmann AM, DeRouen TA, Galloway DA, Vernon D, Kiviat NB. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. *New England journal of medicine*. 1992 Oct 29;327(18):1272-8.
2. Pirota MV, Ung L, Stein A, Conway L, Mast C, Fairley CK, Garland SM. The psychosocial burden of HPV-related disease and screening interventions. *Sex Transm Infec*. Published Online August 24, 2009; doi: 10.1136/sti.2009.037028

Introduction :

- Line 7, page 5 should say "...common viral sexually transmitted infection.."

Thank you for calling to attention. The sentence now reads 'HPV types 6 and 11 alone are estimated to cause the majority of common viral sexually transmitted infections'.

Methods :

- It is unclear the usefulness of the long paragraph on "Participating physicians" –they are not the participants of the study. Did they administer the questionnaire?

Physician selection criteria has been deleted.

The survey was administered at the offices or clinics of the participating physicians. A paragraph explaining the same has been added.

'All data collection for this study was conducted in the offices or clinics of the participating physicians. Participant physicians invited their patients for study participation as part of routine practice by asking their patients if they would be willing to participate in a survey and giving them a patient informed consent form with a short description of the survey. The physician provided verification on the survey regarding to which group the patient belonged (GW or control group) and gave them the survey to

complete in the physician's office. Once the survey was completed, the patient's survey was placed in a sealed envelope and left at the physician's office to be sent or picked up by a research coordinator. Physicians were provided with a patient tracking sheet with a quota of which patients were expected to be recruited per patient group'. Page 6-7, lines – 152-174

- It is unclear how the 150 male and 250 female patients were selected. Was it at random? Consecutive?

A simple convenience selection method was used to select the patients. Page 22, lines 447-448

- On page 8, line 49 – it is unclear why the women with GW AND with precancerous lesions or abnormal pap were excluded as the results tables combine women who had GW only or abnormal pap/precancerous lesions (i.e. the results tables did not present data by discrete disease groups of CIN vs. GW).

This was done to evaluate difference in emotional health between women with GW and those with other selected CIN. Please see result in appendix (Table A-3. HIP Questionnaire Scores by Female Patients and selected HPV-related diseases in South Korea. Supplementary information.

- How was the status of the women with HPV related disease determined? Self report?

The survey was a self-reported based survey. Patients provided the initial status assessment which was then verified by the provider.

- There is no information as to how the controls (i.e. those without GW/HPV related disease) were selected. Were they recruited from the same clinics as men and women with GW?

Yes, the control patients were all recruited from the same clinic as patients with GW. Patients with normal Pap result and no definitive cervical therapy within the past year were added in the control group. A sentence stating the same has been added on page 6, line 155-157. "The physician provided verification on the survey regarding to which group the patient belonged (GW or control group) and gave them the survey to complete in the physician's office.

- A rationale for inclusion of all three quality of life tools is missing. Why choose all three - What is the role and interplay of each? Do some of the tools address different aspects of psychosocial stress/anxiety? Were each of them validated?

Three validated surveys were used to assess different aspects of the psychological response to the disease diagnosis. For example, the HPV Impact Profile (HIP) survey evaluates worries and concerns, emotional impact, sexual impact, self-image, partner transmission, physician interaction, and control/life impact. The CECA survey evaluates emotional and sexual activity. The EQ-5D measures Health Related Quality of Life.

- How are the different QOL systems scored? It may be useful to have an example of some of the questions asked.

- HIP: The response for each item is a 0 (lowest impact) to 10 point (highest impact) discretized analogue scale; and the scale uses visual-spatial, numeric and verbal descriptive anchors to assess subject responses.

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

- EQ-5D: This questionnaire has two parts, the descriptive part and the thermometer or Visual Analogue Scale (VAS). VAS ranges from 0 (worst imaginable health state) to 100 (best imaginable

health state). Page 9, Lines 223 -238

“participants completed the three validated questionnaires; HIP (HPV Impact Profile), CECA (Cuestionario Específico para Condiloma Acuminado in Spanish– ‘Specific questionnaire for Condylomata Acuminata’) and EQ-5D (EuroQol-5 Dimension) surveys, which were translated to the Korean language and culturally pre-tested” page 8, lines 212-215

- Was the questionnaire administered before or after GW diagnosis? Who administered the questionnaire?

Questionnaires were administered after GW diagnosis. The physician administered the questionnaire.

Results:

- Is there any reason for a higher number of women vs. men?

Statistical differences between groups for the mean value of certain questionnaire items or domains could be achieved if the sample size was adequate to detect differences with a pre-specified statistical power. This required some knowledge of previous outcomes in similar studies. According to published data from Wang et al (2010), a study of 50 female subjects demonstrated the ability to detect relatively large differences between the GW group (n=50) and the normal Pap study group (n=51) (mean scores of 62.5 versus 28.2, respectively (p=0.0001)). It was reasonable therefore to plan a similar sample size for females surveyed and to plan a 50% additional sample size (50% of 50 which is 25) to address the gender differences for males. The male sample for the psychosocial impact information was estimated to be at least 75 (50 + 25 additional) males in each of the 2 groups (total n=150) and at least 50 females in each of the 5 groups (total n=250).

Reference:

Wang KL, Jeng CJ, Yang YC., et al. The psychological impact of illness among women experiencing human papillomavirus-related illness or screening interventions. JPOG 2010.

- Line 35 on page 11 needs to be revised –not all of these factors are presented in Table 1.

Thank you for calling it to attention. The sentence is revised and now reads ‘Table 1 shows age, marital status, highest educational degree, and sexual activity according to gender and HPV diagnosis status. Page 10, lines 258-259.

- Could the authors report on any statistically significant difference between males and females with respect to sexual behaviour and GW diagnosis? For example, line 54 “Male GW patients reported a younger age at first sexual intercourse.” – could the authors provide a p-value? It also appears that a higher proportion of females never used condoms compare to males- could this be statistically significant? And could this have any bearing on the results?

The main focus of this manuscript is to understand QoL within sex groups – males with and without disease and females with and without disease – not to compare males and females. Hence we did not test for statistical significance across sex groups. The variables “age of first sexual intercourse” and “use of condoms” were not compared between the male and the female patients, so we do not have p-values, and cannot state if there was any statistical significance, and if it has any bearing on the results.

- Table 3: should the row titled “Women with GW” not be “Women with HPV related disease”? as per Table 1 and Table 2? The methods indicated (page 8, line 49) that women would be categorised according to whether they had discrete outcomes of GW or HPV related disease (abnormal pap smear). Would the author expect that these discrete groups of women would have similar health

related quality of life scores? Would it not be justifiable to present the HIP, CECA and EQ-5D scores separately for women with GW and women with HPV related disease ?

Table 3 has been revised to read “HIP Questionnaire Scores of Participating Patients by GW and HPV related Disease Diagnosis in South Korea” and the row has been changed from “Women with GW” to “Women with HPV-related disease”

Also, the HIP Questionnaire Scores were used to evaluate the discreet HPV-related disease in the female patients (please find result in the supplementary information).

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

- It would be helpful if Tables 3, 4 and 5 had footnote explaining how the scoring system is established; e.g for Table 3: HIP items range from 0 (lowest impact) to no to little impact (mean HIP score <40)...etc.

The following has been added to Tables 3, 4 and 5 (now 2, 3, and 4) as footnote:

‘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)

- Table 3: it is interesting that 60% of women with no GW reported moderate impact in the HIP scoring. What could explain this score in the control group (again, this argues for a better description, explanation of how the controls, i.e. women without GW/HPV related disease, were selected).

- There was a greater proportion of women with GW (or HPV related disease) who reported feeling moderately depressed compared to women without GW/HPV related disease – but the same association was not observed among men. Could this be influenced by the whether women had HPV related disease or not?

Literature suggests that the psychosocial impact of sexually transmitted disease diagnoses may be greater for women than for men. The origin of these differences is not clear, but they may be due to sexual infectivity and reproductive health.

References:

Woodhall S, Ramsey T, Cai C, et al. Estimation of the impact of genital warts on health-related quality of life. *Sex Transm Infect.* 2008;84(3):161-6.

- Line 13, page 19 has an error link to Table. Similarly line 56 on same page

Thank you for calling it to attention. It has been addressed

- Table 1 and Table 2 could be combined in a single table.

Thank you for your suggestion. They have been combined under Table 1: Socio-demographic Characteristics and Sexual Activity of Survey Participants in South Korea by Gender and GW Diagnosis (men) or HPV-related Diseases (women).

Discussion

- Line 7, page 20 should say “This cross-sectional study estimated the psychosocial burden of GW and HPV related disease in South Korea...”

Thank you for calling it to attention. It has been addressed

- Line 40, page 20 “women reported poorer health status following a GW diagnosis than a CIN diagnosis”, and Line 5, page 21 “Female GW patients suffered a major impact compared to those with other selected HPV-related diseases”. This appears surprising– why might this be?

These results are consistent with those previously reported by Wang SM et al in China. According to this study, women with GW had the highest mean HIP scores (52.2), showing a high psychological impact, followed by the group with precancerous cervical lesions (48.6), HPV+ after abnormal Pap (45.8), abnormal Pap test result without HPV test (44.1), HPV- after abnormal Pap (43.1), while women with normal Pap reported the lowest impact (33.1). Another study performed by Wang et al in Taiwan reported that significant psychological impact is found in women diagnosed with abnormal Pap, CIN, positive high-risk HPV test, and GW compared to women with a normal Pap; women with GW had the highest psychological impact scores.

References:

1. Wang KL, Shi JF, Kang DJ, Song P, Qiao YL; Chinese HPV study group. Impact of human papillomavirus-related lesions on quality of life: a multicenter hospital-based study of women in Mainland China. *Int J Gynecol Cancer* 2011;21:182-8.
2. Wang KL, Jeng CJ, Yang YC, Chen CA, Cheng WF, Chen TC, et al. The psychological impact of illness among women experiencing human papillomavirus-related illness or screening interventions. *J Psychosom Obstet Gynaecol* 2010;31:16-23.

However, as far as we know, there are no studies that have looked at why female GW patients suffered a major impact compared to those with other selected HPV-related diseases. We suspect that the presence of the overt GW lesions for these patients might be the foremost reason for the major impact.

- It would it be useful to discuss the implications of these findings in relation to currently available HPV vaccines and decision making on which vaccines to include in national programmes, i.e. bivalent vs. quadri/nonavalent?

The following line has been added on Page 22 lines 462-466 “Prevention of all HPV-related disease, cancers, and non-cancerous lesions is important. Vaccines that have broad protection against multiple HPV types should be considered. In addition, the results of this study can also help guide in directing the development of HPV-related vaccines which can be included in national programs”

- Limitations – Line 47 – could this not be an overestimate of the true effect?

Yes, there is the potential for overestimation of the true effect as patients were selected from physicians' offices that are known to manage GW cases

- Conclusion: “this study highlights the lack of information on the psychosocial impact of GW on HRQoL” – could the authors consider other evidence available including Tan et al (*Sex Health*. 2014 Sep;11(4):), Qi et al (*BMC Public Health*. 2014 Jul 21;14:739.), Dominiak-Felden et al (*BMC Public Health*. 2013 Nov 12;13:1065.)

Thank for your recommendation. The aforementioned studies have been included in the conclusion section of the manuscript and it reads “Although recent studies have looked at the psychosocial

impact of GW on HRQoL in other places like China, Singapore and UK, this study highlights the psychosocial impact of GW on HRQoL for infected patients in South Korea.

VERSION 2 – REVIEW

REVIEWER	Sarah McQueary Flynn University of the Cumberland, USA
REVIEW RETURNED	04-Feb-2018

GENERAL COMMENTS	This revision is much improved, however I'm not comfortable recommending acceptance unless test statistics are reported—not just p values.
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REVIEWER	Caio Cavassan de Camargo Universidade do Sagrado Coração
REVIEW RETURNED	09-Feb-2018

GENERAL COMMENTS	Although the article provides relevant information regarding the psychosocial impact of HPV in men and women, the sample was observed in 2011, that is, with respect to the profile of patients expressing warts or HPV-related disease, possibly not portrays the current scenario. In view of updates related to vaccination and decreased expression of HPV-related disease, the study depicts a scenario from 7 to 10 years ago. Some current studies report that HPV causes low psychosocial impact in the population even when related to warts.
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REVIEWER	Helen Kelly London School of Hygiene and Tropical Medicine United Kingdom
REVIEW RETURNED	29-Jan-2018

GENERAL COMMENTS	<p>Some additional comments in response to the Response Letter :</p> <p>1. Was the questionnaire administered before or after GW diagnosis? Who administered the questionnaire? Questionnaires were administered after GW diagnosis. The physician administered the questionnaire.</p> <p>Reviewer comment: perhaps this ought to be stated in the methods section?</p> <p>2. Table 3: it is interesting that 60% of women with no GW reported moderate impact in the HIP scoring. What could explain this score in the control group (again, this argues for a better description, explanation of how the controls, i.e. women without GW/HPV related disease, were selected).</p> <p>Reviewer comment -I think this comment was not addressed?</p> <p>3. Line 40, page 20 “women reported poorer health status following a GW diagnosis than a CIN diagnosis”, and Line 5, page 21 “Female GW patients suffered a major impact compared to those with other selected HPV-related diseases”. This appears surprising– why might this be?</p> <p>Reviewer comment: It is still not clear why women reported poorer health status following a GW diagnosis than a CIN diagnosis. Could</p>
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	<p>the authors not expand on why this might be the case? Should this not be mentioned at least in the Discussion, that there may other reasons not yet known or explored to explain this?</p> <p>3. "In addition, the results of this study can also help guide in directing the development of HPV-related vaccines which can be included in national programs"</p> <p>Reviewer comment: It is not clear how the findings in this manuscript can help guide development of novel HPV vaccines (given that current vaccines target HPV6 and 11). Perhaps authors could expand?</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Sarah McQueary Flynn

Institution and Country: University of the Cumberlands, USA

Please state any competing interests: None declared

Please leave your comments for the authors below

This revision is much improved, however I'm not comfortable recommending acceptance unless test statistics are reported—not just p values.

Effects size has been added to Tables 2 (HIP Questionnaire Scores of Participating Patients by GW and HPV-related Diagnosis in South Korea) and 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).

Table 1 compares the baseline characteristics based on GW diagnosis whereas table 3 evaluates the EQ-5D Descriptive System Results by Male and Female patients with and without GW and Selected HPV-related Diseases in South Korea. Since these tables descriptively evaluated the baseline characteristics and the EQ-5D scores, effect sizes were not included for these tables.

Reviewer: 2

Reviewer Name: Caio Cavassan de Camargo

Institution and Country: Universidade do Sagrado Coração

Please state any competing interests: None declared

Please leave your comments for the authors below

Although the article provides relevant information regarding the psychosocial impact of HPV in men and women, the sample was observed in 2011, that is, with respect to the profile of patients expressing warts or HPV-related disease, possibly not portrays the current scenario. In view of updates related to vaccination and decreased expression of HPV-related disease, the study depicts a scenario from 7 to 10 years ago. Some current studies report that HPV causes low psychosocial impact in the population even when related to warts.

We agree with the reviewer that the data in our study dates to 2011. However, as far as we know this is the first study that have looked at the psychosocial impact of GW and HPV-related disease on patients' quality of life within the South Korean population. Our study highlights the impact of GW on the psychosocial well-being of the patients.

Furthermore, current research on GW and HPV related disease is needed within this population to understand the impact on patient's quality of life and mental health. Using our study as a baseline,

future studies on the psychosocial impact of GW and HPV-related disease can evaluate the impact of interventions, like health education, counselling and HPV vaccine use within the population. In addition to evaluating how the psychosocial impact of GW and HPV-related disease on patients' quality of life has changed within the South Korean population.

The following sentence has been added in the manuscript on Page 19, line 298 "To our knowledge, this is the first study that has looked at the psychosocial burden of GW and HPV-related disease on patients' quality of life in South Korea"

Reviewer: 3

Reviewer Name: Helen Kelly

Institution and Country: London School of Hygiene and Tropical Medicine, United Kingdom

Please state any competing interests: None

Please leave your comments for the authors below

Some additional comments in response to the Response Letter:

1. Was the questionnaire administered before or after GW diagnosis? Who administered the questionnaire?

Questionnaires were administered after GW diagnosis. The physician administered the questionnaire.

Reviewer comment: perhaps this ought to be stated in the methods section?

The following sentence has been added on Page 9, line 168-169

"Questionnaires were administered by the participating physician after patients were diagnosed with HPV-related disease"

2. Table 3: it is interesting that 60% of women with no GW reported moderate impact in the HIP scoring. What could explain this score in the control group (again, this argues for a better description, explanation of how the controls, i.e. women without GW/HPV related disease, were selected).

Reviewer comment -I think this comment was not addressed?

Thank you for bringing it to our attention.

The following has been included in the methods section. "The control group was selected from the same clinic as the case group. Physicians provided verification on the survey regarding patient groups (GW or control group) and gave them the survey to complete in the physician's office. The physician sample was divided across primary care physicians (general practitioners and internal medicine), obstetrics/gynecologists, urologists, and dermatologists. The control group consisted of patients who have never had GW or received treatment for it or had surgery or therapy in the genital area and included all other patients from a physician's practice or clinic." Page8 – lines 140-146

The following has been included in the discussion section "This study also observed that 60% of women with no GW reported a moderate impact in the HIP scoring. Reasons for this impact level among these patients were not evaluated. However, there is the possibility that these patients may have had other conditions during presentation at the clinic that may have impacted their HIP score." Page 22-23, lines 371-374

3. Line 40, page 20 "women reported poorer health status following a GW diagnosis than a CIN diagnosis", and Line 5, page 21 "Female GW patients suffered a major impact compared to those with other selected HPV-related diseases". This appears surprising– why might this be?

Reviewer comment: It is still not clear why women reported poorer health status following a GW diagnosis than a CIN diagnosis. Could the authors not expand on why this might be the case? Should this not be mentioned at least in the Discussion, that there may other reasons not yet known or

explored to explain this?

The following has been included in the discussion section

“Previous studies have shown that patients with GW had significantly lower quality of life, and substantial psychosocial burden with higher social stigma – especially when GW infection is symptomatic, visible to the naked eye, and found in the genital region. In addition, a study that compared GW patients with asymptomatic genitourinary internal medicine patients observed that patients with GW had a significantly higher psychological burden because of the GW infection compared to the other patients. The study also observed that infection with GW not only influences the patient’s physical wellbeing but also has a potentially detrimental effect on the patient’s emotions. This could explain the observed poorer health status in GW patients evaluated in this study.” Page 21, lines 336-345

3. "In addition, the results of this study can also help guide in directing the development of HPV-related vaccines which can be included in national programs”

Reviewer comment: It is not clear how the findings in this manuscript can help guide development of novel HPV vaccines (given that current vaccines target HPV6 and 11). Perhaps authors could expand?

Our study highlights the psychosocial burden of GW and HPV related disease on the youth and adults in South Korea. Due to such a large impact, more awareness needs to be created regarding vaccines for these conditions.

The following sentences "In addition, the results of this study can also help guide in directing the development of HPV-related vaccines which can be included in national programs” has been rephrased to read.

“The results of this study can help direct guidelines for patient counseling and health education and emphasize the need to include HPV vaccines programs as part national vaccine programs. Page 24, lines 409-411

VERSION 3 – REVIEW

REVIEWER	Caio Cavassan de Camargo Universidade do Sagrado Coração/ Brasil
REVIEW RETURNED	25-Apr-2018

GENERAL COMMENTS	Bibliographic references were clearly updated, although there are still some old articles, they refer to the method that was used to develop the study. The subject matter is pertinent and the point involving the diagnosis of HPV associated with the presence or absence of warts in men has been solved
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REVIEWER	Sarah Flynn University of the Cumberland, USA
REVIEW RETURNED	30-Apr-2018

GENERAL COMMENTS	At this time I cannot recommend that this manuscript be accepted for publication. The authors' still do not report test statistics (t values, F values)--which has been my recommendation at every revision. Although I appreciate the reporting of effect sizes, ALL pertinent statistical information needs to be reported. Furthermore, after reading another revision, it has become more clear that the language that suggests causation is used ("GW in mails and HPV-related disease in female patients had a negative
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	<p>impact on patient well being). This was not a randomized controlled design: the HPV related variables were ex-post facto. Therefore, the only language that can properly be used in this paper would be "associated with". It's a possibility that those affected by HPV may have other factors contributing to poor HRQoL (the third variable problem).</p>
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