Prevalence of high-risk HPV in women with biopsy-proven condyloma acuminata*

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ABSTRACT

Objective: To determine the prevalence of HPV high risk positivity among women patients ages 30 to 65 with biopsy-proven external genital warts (condyloma acuminata) specifically for HPV 16, HPV 18, and for other high risk types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66/68, 73, and 82.

Methodology: A cross-sectional study was conducted at the Department of Obstetrics and Gynecology Out-Patient Services of the Philippine General Hospital involving 57 women, 30 to 65 years old, with biopsy proven external genital warts or condyloma acuminata. These women underwent human papillomavirus (HPV) genotyping test for the high risk types (HR-HPV) from cervical samples using the automated polymerase chain reaction (PCR) technology.

Results: Fifteen out the 57 subjects had at least one of the HR-HPV types for an overall prevalence of 26.3%. Of the 15, 8 (53.3%) had at least 2 HR-HPV types with one subject having the most number of types at 6. Among the strains, the most common is HPV 51 and 52 each with a prevalence of 8.77% followed by HPV 53 and 59 at 7% each. HPV 16 and 18 each only had a 3.5% prevalence the same as HPV 58, 73, and 82. HR-HPV positivity was most common in the 30 to 39 age group (80%), and equally in the nulligravid and the secundigravid (40% each). None had current or past cigarette-smoking history and 33% had some form of hormonal contraception.

Conclusion: The overall prevalence of high risk HPV (HR-HPV) among these 57 Filipino women with external genital warts is 26.3%. The higher prevalence of HPV 51, 52, 53, and 59 over HPV 16 and 18 in this group does not follow the usual epidemiological characteristics reported about this disease.

INTRODUCTION

The human papilloma virus (HPV), a non-enveloped, double-stranded DNA virus belonging to the Papilomaviridae family, with more than 100 types, has a wide spectrum of disease associated with it. Disease ranges from latent HPV infection detectable only by molecular techniques to external genital warts, intraepithelial neoplasias, and at the extreme are the HPV-associated neoplasias.

The three-year cumulative risk of getting HPV infection among young women in the US ages 15 to 19 who recently became sexually active is 44%.[1] Very common among these is genital warts or condyloma acuminata. Its exact number, however, is not known. In the United States, 13% of Americans attending Sexually Transmitted Disease (STD) clinics have genital warts.[2] For a 5-year period from 2013 to 2017, 309 new cases of external genital warts were seen by the OB-GYN Infectious Disease Service of the Philippine General Hospital plus another 205 associated with pregnancy.[3]

The most common HPV types associated with genital warts are HPV 6 and 11 which are established low-risk types of the virus. They account for 90% of the cause of external genital warts. Nonetheless, its transmission remains through sexual contact or through genital skin contact. Genital warts are generally believed to be not associated with cervical cancer.

Cervical cancer, the second most common cancer among women, has for its necessary cause the HPV. The culprit HPV types here are the high risk types.[1] A meta-analysis by the International Agency for Research on Cancer (IARC) included more than 10,000 cervical cancer cases from 85 published studies. The most common HPV types identified in cervical cancer were in order of decreasing prevalence HPV 16, 18, 45, 31, 33, 58, 52, 35, 59, 56, 51, 68, and 39. Over two-thirds of cervical cancer cases were associated with an infection of either HPV 16(51%) or HPV 18 (16.2%).[4] The presence

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of HPV DNA in cervical neoplasia makes it the necessary cause of cervical cancer.

Other HPV-attributable cancers include cancers of the vulva, vagina, anus, penis, and oro-pharyngeal. The percentage of HPV causation for these cancers are lower than that for the cervix: oropharyngeal (12%), vulva and vagina (40%), and anus (90%).[5]

Many women would have contracted HPV infection in their lifetime but not all will develop cervical cancer. A number of other co-factors are likely to be involved in the disease process. These include environmental or exogenous cofactors including hormonal contraceptives, cigarette smoking, parity, and co-infection with other sexually transmitted agents; viral cofactors including other HPV types, viral load and integration; and host cofactors including endogeneous hormones, genetic and immune-related factors.[6]

The presence of external genital warts or condyloma acuminata is not often mentioned as a possible co-factor for the development of cervical cancer. Though the former is related predominantly to low-risk HPV types, they also are transmitted through sexual contact just like the high risk HPV types. Infection with these non-oncogenic types may facilitate co-infection.[7] Co-infection with multiple HPV types is possible and may have both low and high risk types.[8] Large cohort studies conducted in Europe on genotypes in external genital warts have shown that both low and high risk types are also present in these lesions.

The French EdiTH IV study showed the incidence of genital warts at 107/100,000 person-years. HPV 6 was most common at 69% followed by HPV 11 at 16%. Oncogenic high risk types were also present including HPV 16 (9%), HPV 51 (8%), HPV 52 (7%), HPV 66 (6%), HPV 53 (5%) HPV 31 and 18 (3% each).[9] The Swedish cohort with 621 subjects showed HPV 6 was most common at 62% followed by HPV 16 (high risk type) at 13% and HPV 11 at 10%.[10] High risk HPV types were present in 45% of females.

Knowing that oncogenic high risk types may also be associated with external genital warts, does this mean that these lesions are also markers of future malignancies? Big cohort studies conducted in Europe have also looked into this risk of malignancy with condyloma acuminata.

There are limited data as to the HPV genotypes associated with external genital warts in the Asian region including the Philippines. This study aimed to determine the prevalence of HPV high risk positivity among Filipino women 30 to 65 years old with histologically- proven external genital warts or condyloma acuminata.

MATERIALS AND METHODS

Setting: The study was conducted at the Out-Patient Clinic of the Department of Obstetrics and Gynecology of the Philippine General Hospital.

Study Population: The study included women with biopsy proven external (vulvovaginal and perineal) genital warts ages 30 to 65 after appropriate informed consent were taken. Excluded were women with the following conditions: 1) pregnancy; 2) immunocompromised including HIV infected, on chronic steroid use, and organ transplant patients; 3) patients with known and biopsy-proven cervical cancer; 4) patients with epithelial cell abnormality on conventional or liquid-based Pap smear (Atypical squamous cells of undetermined significance to squamous cell carcinoma and adenocarcinoma) from her latest Pap smear; 5) have received at least one dose of any of the two commercially available HPV vaccines (bivalent, quadrivalent or nonavalent).

The external genital warts' gross morphology ranged from the soft, filiform, mucosal lesions in the labia minora to the fungating, plaque-like, raised lesions in the vulva. Sizes were from 5 to 10 mm to big ones more than 3 cms.

Sample Size: Using sample size for frequency in a population (proportion)[11] and the reported Philippine data on the incidence of HPV infection of any type at 9.2%[12], the sample size needed for 80% confidence level is at least 55. The study had a total of 57 subjects.

Study procedures: Women who fulfilled the inclusion criteria and had informed consent had cervical samples taken using the sampler of the commercially available (GeneXpert) automated real time PCR HPV genotyping and sent to the laboratory at room temperature transport. The results were reported as positive for one or more of the following HPV high risk types (HR-HPV): 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66/68, 73, and 82.

Women who tested positive for the high risk types were referred to the Gynecologic Cancer Detection Clinic for surveillance and further management but was no longer part of the study.

RESULTS

Fifty seven women participated in the study. Table 1 shows the socio-demographic characteristics of the women. The average age was 37.35 with a range of 30 to 65. One third of the patients were nulligravid. The most number of pregnancies was 10 in one subject. Fifty-six percent of the subjects had their first coitus between

Table 1. Socio-Demographic Characteristics of the Participants

Characteristics	Number (n=57)	Percentage (%)
Age		
30-39	39	68.4
40-49	14	24.6
50-59	1	1.8
60-65	3	5.3
Gravidity		
0	19	33.3
1	7	12.3
2	14	24.6
3	8	14.0
4	4	7.0
5	4	7.0
>5	1	1.8
Age at first coitus		
15 to 19 years old	20	35.1
20 to 29 years old	32	56.1
30 years old and above	5	8.8
Number of lifetime partners		
1	33	57.9
2	14	24.5
3	5	8.8
>3	5	8.8
History of use of hormonal contraception (Oral/injectable/both)		
Yes	20	35.1
No	37	64.9
History of cigarette smoking (current/past)		
Yes	7	12.3
No	50	87.7

the ages 20 and 29 while 20% had it earlier at ages 15 to 19. Fifty-eight percent had only 1 lifetime sexual partner. The most number of lifetime partners was 10 found in 2 subjects. Sixty-five percent did not have history of use of hormonal contraceptives, either oral or injectable. More than 87% did not have a history of cigarette smoking whether past or current.

There were 15 subjects who had at least one of the tested HR-HPV positive giving an overall prevalence rate of 26%. Table 2 shows the prevalence of each of the HR-HPV types. Among the 15 subjects, 8 (53.3%) had 2 or more HR-HPV types present with the most number at 6 types in 1 subject. Among the different high-risk types of HPV, the most frequent in the 15 subjects with positive results were HPV 51 and 52 (8.77% each) followed by HPV 53 and 59 (7% each). HPV 16 and 18 come in third at 3.5% each together with HPV 58, 73, and 82.

Table 3 shows the socio-demographic characteristics of the 15 who had HR-HPV positive results. Most (12 out of 15, 80%) of those who had positive results belong to the 30 to 39 year old age group. Forty percent were nulligravid and another 40% were secundigravid. Three of the subjects had their first coitus at age less than 20. Two-thirds of the subjects who tested positive had only 1 lifetime partner. None of those positive had a history of cigarette smoking. Six (40%) had a history of hormonal contraceptive use.

DISCUSSION

The results of the study showed that the overall prevalence of HR-HPV positivity among this group of Filipino women seen at the outpatient clinic of a government tertiary hospital with biopsy-proven condyloma acuminata at 26.3% is lower compared to

Table 2. Prevalence of the HR-HPV types among those positive (n=15)

HPV type	Frequency (n=15)	Percentage (%)
Number of high risk types present		
1	7	46.7
2	3	20
3	3	20
4	1	6.7
5	0	0
6	1	6.7
HPV 16	2	3.5
HPV 18	2	3.5
HPV 33	0	0
HPV 35	1	1.75
HPV 39	0	0
HPV 45	1	1.75
HPV 51	5	8.77
HPV 52	5	8.77
HPV 53	4	7
HPV 56	1	1.75
HPV 58	2	3.5
HPV 59	4	7
HPV 66/68	1	1.75
HPV 73	2	3.5
HPV 82	2	3.5

Table 3. Socio-Demographic Characteristics of those who tested positive for any of the HR-HPV types.

Case	Age	Gravidity	Age of First Coitus	Number of Lifetime Sexual partners	History of hormonal contraceptive use	History of cigarette smoking (past or current)	HR-HPV types positive
1	30	0	22	8	No	No	52
2	50	4	17	1	Yes	No	16, 52
3	34	2	16	10	No	No	59
4	30	0	25	1	No	No	35, 58, 82
5	38	2	19	2	Yes	No	52
6	30	0	20	1	Yes	No	51, 52, 59
7	34	0	34	1	No	No	52
8	30	0	29	1	No	No	18, 51, 53, 59, 66, 68, 73
9	30	0	21	1	No	No	51, 56
10	41	0	27	1	No	No	53
11	37	2	23	3	Yes	No	53
12	30	2	18	1	No	No	18, 59
13	39	2	17	2	Yes	No	45
14	33	2	21	1	Yes	No	16, 51, 53, 58, 73
15	30	1	21	1	No	No	16, 51, 73

those reported by the French (41%) and the Swedish (45%) studies. Does this mean that condyloma acuminata is a less significant disease among our Filipino women? The disease burden of HPV infection continues to be significant. Twenty-six percent may be lower but it still means 1 in 4 Filipina with external genital warts ages 30 and above likely has persistent high risk-HPV infection if we follow the premise of the 2012 US screening guidelines[13] that those women in that age group who on HPV testing carry any of the HR-HPV type have not cleared that particular infection. This persistent HPV infection gives the biggest risk of developing cervical and other HPV-associated cancers in the future.

One of the bigger cohort studies on cancer risk among patients with condyloma acuminata was conducted in Sweden involving both men and women and median follow-up of 13 years.[8] A total of 9,286 women were included. Standard incidence rates (SIR) were highest for cancer of the vagina (12.0) and vulva (10.2) but not for cervical cancer. Carcinoma-in-situ of the cervix SIR was at 1.9. The increased detection and treatment of the carcinoma-in-situ probably resulted to less cervical cancer.

The biggest cohort study to date on the same topic was conducted in Denmark with median follow-up also of 13 years. A total of 32,422 women were included. Similar to the Swedish study, an increased in SIR was reported for cancer of the vulva (14.8) and the vagina (5.9) but not for cervical (1.5).[14] These 2 big cohort studies show evidences of association of external condyloma acuminata more for the vulvovaginal cancers but not much for cervical.

In Asia, the one which reported the risk of malignancy among their men and women with genital warts is Taiwan.[15] For a 14-year period, 21,763 were diagnosed with genital warts. In the same time period, 1,002 cancer were recorded among patients with the genital warts. The SIR for HPV-related cancers was 9.74 (95% CI 3.7-15.77). Most cancers developed within 10 years after genital warts diagnosis.

It is imperative, therefore, that the 15 women included in this study who tested positive for any of the HR-HPV types be followed up for early detection of any premalignant or malignant lesions of HPV-related cancers.

Another important finding in this study that needs to be emphasized is the types of HR-HPV present which is not the usual HPV 16 and 18 but other less common strains like 51, 52, 53, and 59. As reported by the International Agency for Research in Cancer (IARC) in 2003, the most prevalent HR-HPV among Filipino women with squamous cell carcinoma of the cervix is HPV 16 (43.1%) followed by HPV 18 (27.9%) and third is HPV 45 (15.7%).[16] The report of this present study, though with limited number of subjects, showing other strains outside of HPV 16, 18 and 45 as being more common, will make one realize the limitations even of preventive HPV vaccines. Among the most number of HR-HPV strains reported in the present study - HPV 51, 52, 53, and 59, only HPV 52 is covered by the nonavalent vaccine. Screening and follow-up remain very important.

This study which aimed to establish the prevalence of HPV high risk positivity among Filipino women 30 to 65 years old with histologically proven external genital warts (condyloma acuminata) hopes to become a first step in answering the question "Can the presence of external genital warts in Filipino women 30 to 65 years of age then be added as a co-infection which can predict the development of cervical cancer and other HPV-related cancers in the future?" and "Are Filipino women with external genital warts more likely to develop these cancers?" Future studies should follow these women with high-risk HPV types as a cohort and see whether they will be manifesting HPV-related cancers in the future.

CONCLUSION AND RECOMMENDATION

This study showing a 26.3% overall prevalence of HR-HPV among the women with external genital warts or condyloma acuminata ages 30 to 65 is an important first step in the research process dealing with the burden of this disease. The most common HPV strains in this group, HPV 51, 52, 53, and 59 are of utmost importance because these are new findings not reported in past Philippine series of the most common HR-HPV strains. There is a need to follow up these 15 women whether in the context of a study or not. Continuing the study to add more subjects to attain a 95% confidence (at least 129 subjects) can also be done. ■

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