Co-infection of human papillomavirus and other sexually transmitted bacteria in cervical cancer patients in the Philippines

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ARTICLE INFO

Keywords:
Cervical cancer
Human papillomavirus
Ureaplasma
Mycoplasma
Chlamydia
Philippines

ABSTRACT

Cervical cancer is the fourth most common cancer in women globally. Based on several epidemiologic studies, human papillomavirus is strongly associated with cervical neoplasia. Aside from HPV, other bacterial infections in the genital tract were associated with cervical neoplasia. This study aimed to determine the prevalence of HPV infection; and co-infection with Ureaplasma spp., Mycoplasma spp., Chlamydia trachomatis, and Neisseria gonorrhoeae in Filipino cervical cancer patients. Forty-four patients (28 patients with cervical carcinoma and 16 patients with non-malignant cervix) who consulted in the Philippine General Hospital from 2016 to 2017 were included in this study. HPV genotyping and genetic detection of Ureaplasma spp., Mycoplasma spp., C. trachomatis, and N. gonorrhoeae were done using different PCR assays. The prevalence of HPV 16/18/33/52 was 75% in cervical cancer patients and 25% in control patients. Infection with HPV 16/18/33/52 was significantly associated with having cervical cancer (OR: 9.00; 95% CI: 2.18–37.18; p = 0.0024). HPV-16 was the most prevalent HPV genotype among Filipino cervical cancer patients. HPV-18 and HPV-52 were only detected from cervical cancer patients. Among HPV-positive patients, we noted a 22.73% co-infection with Ureaplasma spp. and 9.09% co-infection with Mycoplasma spp. To our knowledge, this is the first study on the co-infection of HPV and sexually transmitted infections among cervical cancer patients in the Philippines.

1. Introduction

Cervical cancer is the fourth most common cancer in women, with an estimated 604,000 new cases and 342,000 deaths worldwide in 2020. It is the leading cause of cancer death in Southeast Asian countries, including the Philippines. Persistent high-risk human papillomavirus (HPV) infection is a known risk factor for cervical cancer (Sung et al., 2021). A study conducted by Ngelangel et al from 1991 to 1993 in the Philippines showed that HPV DNA was present in 93.8% of patients diagnosed with squamous cell carcinoma and 90.9% of patients with adenocarcinoma/adenosquamous. Fifteen different HPV types were detected in squamous cell carcinoma, while six HPV types were detected in adenocarcinoma/adenosquamous carcinoma (Ngelangel et al., 1998).

Interestingly, aside from HPV, other bacterial infections such as C. trachomatis, N. gonorrhoeae, M. hominis, and Ureaplasma spp. were associated with cervical neoplasia (Smith et al., 2002; Ye et al., 2018). C. trachomatis infection was strongly associated with an increased risk of invasive cervical cancer development. Moreover, infection with C. trachomatis was also associated with increased the risk of getting HPV infection as well as HPV persistence (Wallin et al., 2002). Infection with Ureaplasma urealyticum was more prevalent than Mycoplasma hominis in cervical cancer patients. U. urealyticum was present in 57.5% of high-grade squamous intraepithelial lesions, 36.59% of low grade squamous intraepithelial lesions, and only 21.33% in cervical samples with normal cytology (Choi and Roh, 2014). With this strong association of cervical cancer and sexually transmitted infections (STI), there is a need to determine co-infection of STI and HPV among cervical cancer patients. There has been no investigation on co-infection of HPV and STI among Filipino cervical cancer patients.

Thus, this study aimed to determine the prevalence and genotype distribution of HPV infection and identify co-infection with Ureaplasma spp., Mycoplasma spp., C. trachomatis, and N. gonorrhoeae among Filipino cervical cancer patients.
2. Methodology

2.1. Study population

The study is a case-control study of patients with cervical cancer (case) and non-malignant cervix (control) seen at the Philippine General Hospital from 2016 to 2017. Forty-four patients (28 patients with cervical squamous cell carcinoma and 16 patients with nonmalignant cervix) were included in this study. A convenience sampling of patients with histologically confirmed cervical squamous cell carcinoma from the outpatient clinics and wards of the Department of Obstetrics and Gynecology of the Philippine General Hospital in Manila was used to determine the participants in this study. Clinical follow-up data should be complete to be included in the study. Exclusion criteria include antimicrobial treatment within one month before the present research and current pregnancy. The patients in the control group were obtained through convenience sampling of all histologically confirmed non-malignant cervix cases, mostly with chronic cervicitis, in the same institution. This study was approved by the Research Ethics Board of the University of the Philippines Manila (UPMREB Registration No.: 2018-016-01).

2.2. DNA extraction

De-identified formalin-fixed paraffin-embedded (FFPE) samples of cervical tissues from study participants were retrieved from the Section of Surgical Pathology at the Department of Laboratories of the Philippine General Hospital. 5 μm slices of the FFPE samples were used for total genomic DNA extraction according to the protocol of Maxwell® RSC DNA FFPE Kit. Extracted DNA in an aqueous solution was quantified (ratios 260/280 and 260/230) using NanoDrop 2000 Spectrophotometer (Thermo Fisher Scientific, Wilmington, DE, USA).

To evaluate sample adequacy, the human β-globin gene was amplified using 1 μL gDNA, 6.25 μL 2x SYBR Green, 0.625 μL of each of 10 μM primer and 4 μL of deionized distilled water in a total volume of 12.5 μL. The assays were performed using MJ Research, Chromo 4 system (Reno, Nevada, USA). The PCR was conducted with an initial denaturation of 95 °C for 15 min, followed by 35 cycles of 95 °C for 20 sec, annealing temperature of 56 °C for 1 min, extension temperature of 72 °C for 1 min, a final cycle of 72 °C for 4 min. All samples that presented positive for β-globin were used to detect HPV and other sexually transmitted bacteria.

2.3. HPV detection

To detect HPV 16, 18, and 33, Takara PCR Human Papillomavirus Detection Set was used. Control templates for HPV 16, 18, and 33 were used as the positive control. HPV 52 was detected using the type-specific primers used by Fontaine et al. PCR products of samples which turned positive for HPV 52 DNA were purified using NucleoSpin® Gel and PCR Clean Up (Machery-Nagel) and were subjected to DNA nucleotide sequencing using the Big Dye® Terminator 3.1 kit on an ABI 3130 Genetic 219 Analyzer (Thermo Fisher Scientific, MA, 220 USA) according to the manufacturer’s instructions.

2.4. Detection of other sexually transmitted pathogens

For detecting Ureaplasma spp., 16S rRNA gene was used in StepOnePlus real-time PCR instrument (Applied Biosystems, Brazil). Quantification was performed using an absolute quantification technique, based on a predetermined standard curve ranging from 10^7 to 10 DNA copies/μl. The genome dilutions’ Ct (threshold cycle) was plotted against the log number of genome copies and used as input to create the standard curve.

Takara PCR Mycoplasma Detection Set was used according to the manufacturer’s instructions to detect mycoplasma.Nested PCRs were performed using primers MCGp F1 and R1 and MCGp F2 and R2 in Gene Amp PCR System 9700 (Applied Biosystems, Foster, CA, USA). Only 0.5 μL of the first PCR products were used in the second PCR reaction. PCR products (10 μL) were analyzed in 3% NuSieve® 3:1 Agarose gels. All cervical samples were also tested with PCR methodology to detect the targeted DNA of Chlamydia trachomatis and Neisseria gonorrhoeae (dos Santos et al., 2017; Hjelmervoll et al., 2006). The DNA bands were visualized using Stage-2000PV-UV (AMZ System Science, Tokyo, Japan) after ethidium bromide staining. Samples that turned positive were subjected to DNA nucleotide sequencing using the Big Dye® Terminator 3.1 kit on an ABI 3130 Genetic 219 Analyzer according to the manufacturer’s instructions. Samples that turned positive for these pathogens were subjected to DNA nucleotide sequencing using the Big Dye® Terminator 3.1 kit on an ABI 3130 Genetic 219 Analyzer according to the manufacturer’s instructions.

2.5. Statistical analyses

Using Open Epi Software, Pearson’s chi-square test, odds ratios (ORs), and 95% confidence intervals (CIs) were calculated. The results were considered statistically significant if p < 0.05.

3. Results

Baseline characteristics of the patient samples included in this study are presented in Table 1. The mean age of the case group was 52.75 ± 13.16, while the mean age of the control group was 47.31 ± 15.02. Patients with cervical cancer were significantly older than patients in the control group with a non-malignant cervix. No significant differences were found in menarche’s age and first coitus between the two groups. All sociodemographic factors including smoking, alcohol drinking, parity, number of sexual partners, menstrual status, history of oral contraceptive use, and marital status were not associated with having cervical cancer.

There was a significantly higher HPV infection in the case compared to control subjects (Table 2). The prevalence of HPV 16/18/33/52 was 21 (75%) in the case and 4 (25%) in control subjects. Infection with HPV 16/18/33/52 was associated with having cervical cancer (p = 0.0024). HPV-16 was the most prevalent HPV genotype in both groups, with 12 patients positive in the case group and four positive in the control group. There was no significant difference in the individual prevalence of HPV-16 between the two groups. HPV-18 and 52 were only detected from cervical cancer patients, while HPV-33 was not detected in both groups.

There was no significant difference in the prevalence of other sexually transmitted infections (Ureaplasma spp., Mycoplasma spp., and C. trachomatis) between the case and the control group (Table 3). However, it must be noted that the control group used were patients diagnosed with chronic cervicitis. Ureaplasma spp. infection was higher in the case group than the control group, but the difference was not statistically significant. Mycoplasma spp. was only detected in the case group. We saw M. hominis (n = 2) and M. spermatophilum (n = 1) from cervical cancer samples. It is interesting that all positive samples for Mycoplasma spp. were also positive for Ureaplasma spp.

One C. trachomatis was detected from each case and control group (Table 2). However, further analysis revealed that it was only present among HPV-negative subjects (Table 3). Among HPV-positive patients, we noted a 22.73% co-infection with Ureaplasma spp. and 9.09% co-infection with Mycoplasma spp. However, no statistically significant association was found between infections with genital mycoplasmas and HPV infection. N. gonorrhoeae was not detected in all samples included in this study.

4. Discussion

In our study, we noted a 22.73% co-infection with Ureaplasma spp. and 9.09% co-infection with Mycoplasma spp. among HPV-positive
patients. Cervical mycoplasma infection was not associated with HPV infection. This might be due to the low sample size of this study. Previous studies showed that high-density colonization with *U. urealyticum* was significantly associated with HPV infection (Kim et al., 2018; Verteramo et al., 2009). Moreover, *M. hominis* infection was also significantly associated with high-risk HPV infections (Adebamowo et al., 2017). *Mycoplasma* spp. maybe associated with changes in epithelial cells that facilitate entry of HPV virions (Verteramo et al., 2009). More extensive studies are needed to confirm whether an association between *M. hominis* and HPV infection is present.

HPV-16 was the most prevalent HPV genotype in our study. This finding is similar to previous studies conducted in the Philippines, which determined a 38.5% to 40.2% rate of HPV-16 infection among cervical squamous cell carcinoma patients (Domingo et al., 2009; Quek et al., 2013). HPV-52 was only detected among cervical cancer patients in our study. A study by Domingo et al. in 2008 showed HPV-52 infection in cervical squamous cell carcinoma patients but not in patients with adenocarcinoma and normal cytology (Domingo et al., 2009). Another study on Filipino commercial sex workers with abnormal cervical cytology (low- and high-grade squamous intraepithelial lesions and adenocarcinoma in situ) revealed that HPV-52 was the most common (23.2%) HPV type followed by HPV-16 (19.6%) (Miyashita et al., 2009).

HPV-33 was not detected in all subjects in this study. HPV 33 was never determined a 38.5% to 40.2% rate of HPV-16 infection among cervical squamous cell carcinoma patients (Domingo et al., 2009; Quek et al., 2017).

Table 1

| Demographic factors associated with cervical cancer patients. | With Cervical Squamous Cell Carcinoma (n = 28) | With Non-malignant Cervix (n = 16) | OR (95% CI) | p-value |
|---------------------------------------------------------------|---------------------------------------------|-----------------------------------|-------------|---------|
| Age at sample collection                                      | 57.25 ± 13.16                              | 47.31 ± 15.02                     | –           | 0.05    |
| Age of menarche                                               | 15.15 ± 2.31                               | 14.13 ± 1.13                      | –           | 0.07    |
| Age of first coitus Smoking                                   | 18.81 ± 3.26                               | 18.25 ± 1.84                      | –           | 0.47    |
| Smoking                                                       | Yes                                         | 8 (28.57%)                        | 4 (25.00%)  | 0.14    |
| No (ref)                                                      | 20 (71.43%)                                 | 12 (75.00%)                       | (1.01 – 1.92) | 0.44    |
| Alcohol drinking                                              | Yes                                         | 7 (25.00%)                        | 2 (12.50%)  | 4.99    |
| No (ref)                                                      | 23 (75.00%)                                 | 14 (87.50%)                       | (0.43 – 57.58) | 0.20    |
| Parity                                                        | 0–5                                         | 21 (75.00%)                       | 13 (81.25%) | 3.55    |
| ≥6 (ref)                                                      | 7 (25.00%)                                  | 14 (87.50%)                       | (0.23 – 55.89) | 0.37    |
| Number of Sexual Partners                                     | Single sexual partner                       | 16 (53.57%)                       | 11 (68.75%) | 0.58    |
| Multiple sexual partners (ref)                                | 12 (42.86%)                                 | 5 (31.25%)                        | (0.12 – 2.86) | 0.50    |
| Menstrual Status                                              | Menstruating                                | 12 (42.86%)                       | 11 (68.75%) | 0.13    |
| History of OCP use                                           | Yes                                         | 11 (39.29%)                       | (0.02 – 1.08) | 0.06    |
| No (ref)                                                      | 17 (60.71%)                                 | 12 (75.00%)                       | –           |        |
| Marital status                                                | Single                                      | 9 (32.14%)                        | 2 (12.5%)   | 4.50    |
| Married (ref)                                                 | 19 (67.86%)                                 | 14 (87.50%)                       | (0.47 – 42.71) | 0.19    |

Table 2

| HPV types and other sexually transmitted bacterial infections associated with cervical cancer. |
|------------------------------------------------------------------------------------------------|
| No. (%) of study participants positive for HPV DNA and other STI (n = 44) | Univariate Analysis | OR (95% CI) | p-value |
|-----------------------------------------------------------------------------|---------------------|-------------|---------|
| **Infection**                                                               |                     |             |         |
| With Cervical Squamous Cell Carcinoma (n = 28)                              |                     |             |         |
| **HPV infection**                                                           |                     |             |         |
| All HPV Types (HPV 16/18/33/52)                                             | 21 (75%)            | 4 (25%)     | 9.00    |
| HPV-16                                                                      | 12 (42.86%)         | 4 (25%)     | 2.25    |
| HPV-18                                                                      | 6 (21.43%)          | 0 (0%)      | (0.58–8.74) | 0.2414 |
| HPV-33                                                                       | 0 (0%)              | 0 (0%)      | –       |
| HPV-52                                                                       | 5 (17.86%)          | 0 (0%)      | –       |
| **Bacterial Infection**                                                     |                     |             |         |
| Ureaplasma spp. (n = 7)                                                     | 5 (17.86%)          | 2 (12.50%)  | 1.53    |
| Mycoplasma spp. (n = 3)                                                     | 3 (10.71%)          | 0 (0%)      | (0.26–8.93) | 0.6419 |
| C. trachomatis (n = 2)                                                      | 1 (3.57%)           | 1 (6.25%)   | 0.56    |
| N. gonorrhoeae (n = 0)                                                      | 0 (0%)              | 0 (0%)      | (0.03–9.54) | 0.6853 |

Table 3

| Relationship between HPV and other female reproductive tract infections (n = 44). |
|---------------------------------------------------------------------------------|
| Bacterial Infections                                                          | HPV Positive (n = 22) | HPV Negative (n = 22) | Chi-Square | p-value |
| Ureaplasma spp. (n = 7)                                                        | 5 (22.73%)           | 2 (9.09%)            | 1.529      |
| Mycoplasma spp. (n = 3)                                                        | 2 (9.09%)            | 1 (4.55%)            | 0.3577     |
| C. trachomatis (n = 2)                                                         | 0 (0%)               | 2 (9.09%)            | 2.095      |
| N. gonorrhoeae (n = 0)                                                         | 0 (0%)               | 0 (0%)               | –         |

Included and seen in previous studies conducted in the Philippines (Domingo et al., 2009; Miyashita et al., 2009; Ngelangel et al., 1998).

In this study, we noted a 22.73% co-infection with *Ureaplasma* spp. and HPV and 9.09% co-infection with *Mycoplasma* spp. and HPV. Previous studies also showed higher rates of genital mycoplasma infection in cervical cancer patients. Mycoplasmas can promote low-grade chronic inflammatory conditions without killing the cells. Thus, they were thought to be ideal for promoting carcinogenesis (Yacoub et al., 2021). Xiaolei et al. found that the prevalence and the pathogenic load of *U. urealyticum* were significantly higher in the cervical cancer group compared to the control group (Xiaolei et al., 2014). Another study also showed that *M. hominis* was associated with a significantly increased risk of abnormal cervical cytology (Ye et al., 2018).

No significant difference was found in the prevalence of *C. trachomatis* between the case and control groups. *C. trachomatis* infection was associated with increased risk of getting HPV infection and HPV persistence (Jensen et al., 2014). More patients with detectable *C. trachomatis* DNA subsequently developed invasive cervical cancer compared to patients without detectable *C. trachomatis* DNA (Wallin et al., 2002).

This study had several limitations. This study is a retrospective case-control study with potential for recall and selection bias, which could confound the results of this study. This study also had a low sample size of the study may have confounded the results of this study. This is a
preliminary study that will be used in proposing for larger studies in the Philippines. The study only detected four high risk HPV genotypes with already available detection kits in our laboratory. These HPV genotypes were also previously studied and detected among Filipino cervical cancer patients. Lastly, our study used non-malignant cervix with chronic cervicitis as our control group because of the unavailability of cervical biopsies from patients with normal cervix.

5. Conclusion

In conclusion, the overall infection with HPV 16/18/33/52 was significantly associated with cervical cancer. This study revealed that HPV 16 was the most prevalent HPV type among Filipino cervical cancer patients. HPV 18 and 52 were only detected from cervical cancer patients, while HPV 33 was not detected in both groups. Ureaplasma spp. and Mycoplasma spp. were more prevalent in the case group compared to the control group, albeit with no statistical significance. This preliminary data may help encourage future research in this field, which may aid the local health authorities to improve prevention and treatment, to improve the quality of life of women in the Philippines.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by research grants from the UPM NIH, Grant Number NIH2017043 (O. A. G. T. and E. F. L.); JSPS KAKENHI, Grant Numbers JP17H04237 (I. Y.), JP17K10201 (F. N.) and JP18K16788 (M. Y.); the Japan Agency for Medical Research and Development (AMED), JP21fk0108143 and JPfk0108010 (I. Y.).

Authors’ contributions

All authors contributed equally to this work. All authors read and approved the final manuscript.

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