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Sociodemographic and Clinical Factors and Their Association with the Types of Lesion Caused by the Human Papilloma Virus

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Abstract

HPV infection of the lower genital tract is divided into clinical, subclinical and latent. Subclinical infections are more frequent than clinical infections, in both men and women. The objective of this study was to identify the association between the types of lesions caused by HPV and sociodemographic and clinical variables. Subjects were 977 women diagnosed with HPV lesions: LSIL, HSIL or condyloma. The chi-square test was used to verify the association, and p values smaller than 0.05 were considered significant. There was an association between the types of lesions and the age group (p=0.0074), education level (p=0.0011), marital status (p=0.0011), economic status (p<0.01), use of alcohol (p=0.0048) and smoking (p<0.01), the HIV serodiagnosis (p<0.01) and the number of partners (p=0.0077). It was demonstrated in this study that there is an inversion of the prevalence of these types of lesions due to age, which is justified by the persistence and progressiveness of lesions in older women compared to those of a younger age. It was identified that the fewer the years of education, the greater the grade of the HPV lesion. In terms of income, an association was observed with the type of lesion, in that women without a fixed income were the most affected by all types of infection signs. In opposition to the initial hypothesis of this study, there was a greater incidence of women in a stable relationship for all forms of HPV infection, suggesting an exceeding trust in their affective-sexual partner and the consequent unprotected sex behavior.

Keywords: Human Papillomavirus; Women; Nursing

Introduction

Infection with Human Papillomavirus (HPV) is part of a public health problem, as it is considered as one of the more common sexually transmitted infections (STI). It is estimated that approximately 600 million people worldwide have HPV and that around 75-80% of the population acquire the virus at some point in their lives [1].

More than 189 types of Papilomavirus (PV) are known, 120 of which are characterized by affect the human species and 40 can infect the genital tract [2]. The etiological agent is species-specific and is reproduced in the stratified squamous epithelium after performing minor trauma in the upper layers of the epithelium for the inoculation of the virus in the proliferative cells of the basal layer [3].

As regards the classification, HPV infection in the lower genital tract is divided into clinical, sub-clinical and latent. Clinical infection is presented by means of macroscopic lesions called condylomata, sub-clinical is characterized by lesions diagnosed by imaging examinations and latent contemplates the absence of tissue damage, indicating the presence of HPV through the detection of HPV DNA by molecular biology techniques [4].

When the infection is manifested by means of condylomata, lesions may be single or multiple, constrained or diffuse, and of variable size and, depending on the size and anatomical location, may be painful, itchy and flaky. In men, they are located on the glans, sulcus balano-preputial and perianal region; and in women, on the vulva, perineum, perianal region, vagina and cervix. Less frequently, they may be present in extragenital areas such as conjunctiva, nasal, oral and laryngeal mucosa [5].

The sub-clinical HPV infection is more common than the clinical infection in both men and women. Treatment of sub-clinical lesions caused by this agent is not recommended when they are not accompanied by intraepithelial lesions, due to the diagnosis being questionable and no therapy having been able to eradicate the virus. In contrast, in the presence of intraepithelial lesions, the patient should be referred to a specialist service and treatment should be done according to the degree of the disease [5].

In relation to sub-clinical lesions accompanied by intraepithelial lesions, specifically those caused in the cervix, it is emphasized that cervical intraepithelial neoplasia (CIN) is not a type of cancer but a precursor lesion, which, depending on its severity, may or may not develop into cancer. As to its categorization, CIN is divided into grades I, II and III. CIN I is the cellular alteration that affects the more basal layers of the stratified epithelium of the cervix (mild dysplasia). About 80% of women with this type of lesion will present spontaneous regression. CIN II is the existence of cellular disarray in up to three quarters the thickness of the epithelium, preserving the more superficial layers (moderate dysplasia). CIN III is the observation of the disarray in all layers of the epithelium (severe dysplasia and carcinoma

in situ), without invasion of underlying connective tissue. High-grade precursor lesions (CIN II and III) are found most frequently in the 35-49 year old age group, especially among women who have never had Pap smears (Papanicolaou) [6].

In 1988 the Bethesda system was proposed, it was updated in 2001 in order to standardize the description of cervical cytological abnormalities. The term CIN was replaced by the terms low grade squamous intraepithelial lesions (LSIL), equivalent to CIN I and high grade (HSIL), equivalent to CIN II and CIN III [7].

Given the above, the high clinical and epidemiological importance of knowing the factors associated with the processes of infection and oncogenesis related to HPV stands out, since this virus has spread worldwide and has universal distribution, as well as being correlated with the frequency of carcinomas [8].

Therefore the present study aims to identify the association between the types of lesions caused by HPV (LSIL, HSIL, and condylomata: vulvar, vaginal, cervical and perianal) and the sociodemographic and clinical variables.

Materials and Methods

It is a cross-sectional, retrospective study with a quantitative approach, which was conducted at the Department of Infectious Diseases in Obstetrics and Gynecology (SEMIGO), at the Hospital das Clinicas, Faculty of Medicine in Ribeirão Preto, University of São Paulo (HCFMRP-USP).

The study population consists of 977 registries of women attended at SEMIGO who had diagnosis of HPV infection already known and who met the inclusion criteria: 1. Presenting genital HPV infection diagnosed with LSIL, HSIL or condylomata (vulvar, vaginal, cervical and perianal) and 2. Having a full record in the electronic database of the study sector to provide information on the anamnesis taken at the first consultation and information regarding consultations and returns attended.

To collect data, a structured form was designed specifically for this study, undergoing validation, regarding the form and content, by three experts in HPV infection. The variables included were: 1. Sociodemographic variables: age, race, marital status, education, financial situation, alcohol use, tobacco use, illicit drug use and sexual behavior (age at first sexual intercourse, total number of sexual partners, number of sexual partners in the last year, prostitution and sexual orientation) and 2. Clinical: serological tests for HIV, hepatitis B and C, and syphilis.

For sociodemographic and clinical characterization, a search in the electronic database at the study site between March and October 2012 was carried out. Through this search we selected women who had as a reason for attending the consultation, at least one of the following in their records: HPV, vulvar condyloma, vaginal condyloma, cervical condyloma, perianal condyloma, cervical intraepithelial neoplasia grade I (LSIL), II or III (HSIL). The database at the study site was prepared in 2006, but data that was inserted retroactively is included in it. Therefore, data registered for the period from 09/10/1986 to 23/10/2012 were found.

The database was organized in th Microsoft Excel Starter 2010 spreadsheet program, with data validation after double data entry. The study population was characterized by means of descriptive statistics and the data were processed and analyzed using the Statistical Package for Social Sciences (SPSS) version 16.0 for Windows.

To verify the proposed associations, the data were subjected to Chi-Square Test. The quantification of these associations was measured by means of logistic regression models, calculating the gross Oddsratio (OR) with their respective confidence intervals of 95%. Statistical analyses were carried out using the statistical software SAS® 9.0. P values less than 0.05 were considered significant.

The answers "no information" of each sociodemographic and clinical variable were considered as missing and did not enter the analysis. For the association between types of lesions caused by HPV and clinical variables, in the serology items for HIV, hepatitis B, hepatitis C and syphilis, missing, and the answer "no information", the answer "not carried out" were considered. In the "total number of partners" item, just one woman answered that she had never had sex, so it was excluded from the analysis, generating an n of 976 women for this question.

The study was examined and approved by the Research Ethics Committee of the School of Nursing in Ribeirão Preto, University of São Paulo, under protocol No. 1303/2011, taking into account the recommendations of Resolution 196/96 from the National Health Council. The confidentiality and anonymity of the information for all women participants were assured. To query the electronic database, a waiver for the Term of Free and Informed Consent was requested, given that only secondary data obtained from the study of information already collected and recorded in the software was used.

Results

Women who were between 20 to 29 years old were prevalent, 380 (38.89%), 626 were Caucasian (64.54%), 421 completed five to eight years of study (43.09%) 564 were in a stable relationship (57.73%), 509 had no fixed income (52.10%) and 835 did not consume alcohol (85.47%), tobacco, 676 (69.20%) or illicit drugs, 839 (85.88%). Of the total, 391 (40.02%) had HSIL, 349 (35.72%) condyloma and 237 (24.26%) LSIL as lesions caused by HPV.

There was a statistically significant association between the types of lesions caused by HPV and age group (p=0.0074), education (p=0.0011), marital status (p=0.0011), economic status (p<0.01), alcohol use (p=0.0048) and cigarette use (p<0.01). No association was found regarding ethnicity (p=0.0858) and drug use (p=0.7273) (Table 1).

Of the 824 women, 152 (15.56%) were seropositive for HIV, nine (0.92%) for hepatitis B, 22 (2.55%) for hepatitis C and eight (0.81%) for syphilis, 521 (53.33%) had their first sexual encounter before age 16, 727 (75.42%) had one to five sexual partners throughout their lifetime, 916 (95.32%) had less than three sexual partners in the last year, 939 (96.11%) never became prostitutes and 957 (99.06%) were heterosexual.

There was a statistically significant association between the types of lesions caused by HPV and HIV seology (P<0.01) and total number of partners (p=0.0077). There was no association in relation to serology for hepatitis B (p=0.3486), hepatitis C (p=0.2091), syphilis (p=0.0595), first sexual intercourse encounter (p=0.2546), number of sexual partners in the last year (p=0.6311), prostitution (p=0.5291) and sexual orientation (p=0.5980) (Table 2).

Discussion

In the present study, we detected a statistically significant association (p=0.0074) between age and types of lesions caused by HPV, with a predominance of condyloma in women up to 39 years of

| | Type of lesion | | | | |
| | Condyloma | LSIL[1] | HSIL[2] | | |
	n (%)	n (%)	n (%)	*Missing*	*p-value[3]*
Age group (years)					
<16	6 (0.61)	1 (0.10)	5 (0.51)	0	**0.0074**
16|–|19	23 (2.35)	12 (1.23)	12 (1.23)		
20|–|29	142 (14.53)	94 (9.62)	144 (14.74)		
30|–|39	109 (11.16)	71 (7.27)	112 (11.46)		
40|–|49	33 (3.38)	41 (4.20)	80 (8.19)		
50|–|59	27 (2.76)	15 (1.54)	23 (2.35)		
≥ 60	9 (0.92)	3 (0.31)	15 (1.54)		
Ethnicity (cited)					
White	236 (24.33)	141 (14.54)	249 (25.67)	7	0.0858
Non-White	109 (11.24)	96 (9.90)	139 (14.33)		
Education (years)					
0|–|4	31 (3.17)	19 (1.94)	67 (6.86)	16	**0.0011**
5|–|8	144 (14.74)	112 (11.46)	165 (16.89)		
9|–|11	137 (14.02)	87 (8.90)	115 (11.77)		
≥ 12	34 (3.48)	18 (1.84)	32 (3.28)		
Marital status					
Single	132 (13.51)	85 (8.70)	91 (9.31)	11	**0.0011**
Stable Relationship	192 (19.65)	127 (13.00)	245 (25.08)		
Legally Separated	17 (1.74)	17 (1.74)	27 (2.76)		
Widowed	7 (0.72)	8 (0.82)	18 (1.84)		
Financial situation					
With an income	49 (5.02)	40 (4.09)	94 (9.62)	22	**<0.01**
Without an income	211 (21.60)	135 (13.82)	163 (16.68)		
Other	85 (8.70)	61 (6.24)	117 (11.98)		
Alcohol use					
Yes	31 (3.17)	31 (3.17)	66 (6.76)	14	**0.0048**
No	315 (32.24)	202 (20.68)	318 (32.55)		
Tobacco use					
Yes	87 (8.90)	55 (5.63)	151 (15.46)	8	**<0.01**
No	259 (26.51)	181 (18.53)	236 (24.16)		
Drug use					
Yes	49 (5.02)	28 (2.87)	52 (5.32)	9	0.7273
No	296 (30.30)	207 (21.19)	336 (34.39)		

1) LSIL: low-grade cervical intraepithelial lesions, 2) HSIL: high-grade cervical intraepithelial lesions, 3) p-value for the Chi-Square Test

Table 1: Association between sociodemographic variables and the type of lesion in women with genital HPV infection (n=977) treated at the university hospital at Ribeirão Preto-SP, in the São Paulo Countryside, Brazil, 1986-2012.

| | Type of lesion | | | | | |
| | Condyloma | LSIL[1] | HSIL[2] | Missing | | |
	n (%)	n (%)	n (%)	N/R[3]	S/I[4]	p-value[5]
HIV Serology						
Positive	24 (2.46)	47 (4.81)	81 (8.29)	153	0	**<0.01**
Negative	265 (27.12)	154 (15.76)	253 (25.90)			
Hepatitis B Serology						
Positive	2 (0.20)	4 (0.41)	3 (0.31)	46	140	0.3486
Negative	276 (28.25)	187 (19.14)	319 (32.65)			
Hepatitis C Serology						
Positive	4 (0.41)	5 (0.51)	13 (1.33)	59	159	0.2091
Negative	249 (25.49)	181 (18.53)	307 (31.42)			
Syphilis Serology						
Positive	6 (0.61)	1 (0.10)	1 (0.10)	42	0	0.0595
Negative	275 (28.15)	192 (19.65)	322 (32.96)			
First sexual intercourse (years)						
< 16	195 (19.96)	134 (13.72)	192 (19.65)		0	0.2546
16|–|20	129 (13.20)	90 (9.21)	168 (17.20)			
> 20	25 (2.56)	13 (1.33)	31 (3.17)			
Total number of sexual partners (n=976)						

01|–|05	278 (28.84)	176 (18.26)	273 (28.32)	12	**0.0077**
05|–|10	31 (3.22)	39 (4.05)	60 (6.22)		
>10	34 (3.53)	21 (2.18)	52 (5.39)		
Sexual partners in the last year					
< 3	328 (34.13)	226 (23.52)	362 (37.67)	16	0.6311
>3	14 (1.46)	10 (1.04)	21 (2.19)		
Prostitution					
Yes	7 (0.72)	3 (0.31)	10 (1.02)	18	0.5291
No	336 (34.39)	231 (23.64)	372 (38.08)		
Sexual Orientation					
Heterosexual	342 (35.40)	234 (24.22)	381 (39.44)	11	0.5980
Non-heterosexual	2 (0.21)	2 (0.21)	5 (0.52)		

1) LSIL: low-grade cervical intraepithelial lesions, 2) HSIL: high-grade cervical intraepithelial lesions, 3) N/P: not performed; 4) N/I: no information; 5) p-value for the Chi-Square Test

Table 2: Association between clinical variables and type of lesion in women with genital HPV infection (n=977) treated at a university hospital in Ribeirão Preto-SP in the São Paulo countryside, Brazil, 1986-2012.

age and HSIL in women aged 40 years or more. As to the prevalence of types of lesions in women up to 39 years of age, condylomatous lesions had greater frequency (28.7%), followed by HSIL (27.9%) and LSIL (18.2%). While in women aged 40 years or more, HSIL was in first place (12.1%) followed by condylomatous lesions (7.1%) and LSIL (6.0%).

The literature suggests that older women having a higher probability of persistence and progression of lesions when compared to younger women, which could be explained by the transitory nature of HPV infections in women of a lesser age [9]. In addition, older age allows the accumulation of mutations that can lead to malignant transformation [10].

According to a review of studies conducted between the years 1966 and 1996, which defined the strengths and weaknesses of existing research on the natural history of cervical intraepithelial lesions and estimated rates of progression and regression without treatment, most women with LSIL have spontaneous regression of the lesions, with a relative risk of progression to carcinoma of 1.44% and the possibility of regression to normal cytology diagnosis of 47.39% within two years [11]. However, in another study that followed the progress of LSIL and evaluated the treatment received by patients, the rate of regression of LSIL was 87.72% within 18 months [12].

Specifically for this study, the high frequency of HSIL in young women is justified because they are patients treated at a referral center that receives this group of patients for treatment.

A statistically significant association between ethnicity and types of lesions caused by HPV was not identified (p=0.0858). However, it is noteworthy that the variable ethnicity should be interpreted cautiously, especially in Brazil, where racial classification is impaired due to the huge admixture between Europeans, Africans and Amerindians [13].

Despite considerable portion of the population of women with HSIL (38.8%) presented nine or more years of schooling, relatively high educational level, a statistically significant association between low education and HSIL was identified (p=0.0011).

Knowledge is the mediator of attitudes that will benefit, or not, the risk perception on precursor lesions of cervical cancer [14], as well as access to health services and adherence to HIV/AIDS treatment, including interfering in therapeutic understanding due to difficulties in the interpretation of the information provided by the health team and the recognition of the importance of properly carrying out the treatment [15].

However, less access to health services is not just a lack of education and lower demand for patient treatment; it is also related to the adequacy between the supply of services and the demand of the population. Often, the organization of the service does not match the needs and desires of the people assisted, due to the bureaucracy in the carrying out of procedures and scheduling appointments and tests, making health care even more complex and confusing for users with a low level of education [16].

As a likely consequence of the low level of education and most of the women studied developing home activities, a higher frequency (51.5%) of women with no fixed income and statistically significant association (p <0.01) between the absence of income and the presence of condyloma lesions, LSIL and HSIL was observed. Despite the devaluation of domestic work, it is known that through it women contribute to the household income [17], as they manage the goods purchased [18]. As well as lack of information, economic dependence establishes unequal power relations between genders, reducing the bargaining power of women in relation to condom use and therefore the protection against sexually transmitted infections (STIs) [17,19].

It was hoped that the onset of HPV was lower with women in a stable relationship, by being exposed to a lower number of sexual partners, but this group proved to have the greater onset. There was a statistically significant association (p=0.0011) between stable relationships and all forms of the infection, i.e., condyloma, LSIL and HSIL.

One possible explanation for the high prevalence of HPV in married women or women living as married would be the fact that these women, just because they have a stable sex life and trust in a fixed partner, exchange the barrier method of contraception for oral hormonal contraceptives (OHC) [20]. Moreover, it is the ability of the partner to be promiscuous, and thus contribute to a positive association between HPV infection and women in a stable relationship [21].

A statistically significant association was revealed between the type of injury manifested and alcohol use (p=0.0048), indicating higher beverage consumption by women with HSIL.

Drug users often begin their sexual life earlier when compared to non-users, they use condoms less and undertake paying for sex and prostitution [22]. A study conducted by the Center for Epidemiological Research on AIDS [23] observed that the consumption of alcohol and drugs, except cocaine and crack, stimulates sexual activity, because soon after consumption, the impression is that "flirting" gets easier for users, libido increases and sexual performance improves.

A study conducted in Brazil raises the hypothesis that the relationship between drug use and sexual behavior at risk for STIs is not causality, but due to a common type of behavior that they called "liberal" and that it would be applicable for both users of drugs that stimulate sex, such as marijuana and alcohol, as well as for drugs that would not stimulate it, such as cocaine and crack. Yet according to the authors, the relationship between the use of alcohol and drugs and greater sexual activity is linked to the more social behavior of these individuals, who attend bars, clubs and places to knowingly consume these drugs and, at the same time, provide the meeting of sexual partners as a result of the high concentration of people [22].

In addition, added to the increased use of alcohol and drugs, there are other important factors involved in establishing sexual relations with a new partner, such as no condoms available at the time of the sexual act, as it is non-scheduled and there is the fear that discussion about safer sex could interrupt the sexual act or upset the new partner [24].

There was a statistically significant association between cigarette use and the types of lesions caused by HPV (p<0.01), with higher tobacco consumption by women with HSIL.

Tobacco is a risk factor for HPV infection, since, in addition to reducing immune system performance through reduction of Langerhans cells and T_{helper} Lymphocytes in the squamous epithelium transformation of the uterine cervix [25], it causes cell mutations [26,27].

Despite the work done concerning smoking, it is necessary to elucidate the mechanisms that lead it to contribute to cervical carcinogenesis, as well as whether there are differences as to their use, i.e., the number of cigarettes/day, age when started and duration of smoking [28].

It is important to highlight that smoking also suggests a risk factor for the development of lesions in the cervix. American researchers reinforce this assertion in finding high levels of nicotine in cervical lavage samples in studies of nonsmoking women who were exposed to cigarette smoke in their homes [29].

It is known that the number of women smokers is increasing each year, which reinforces the importance of campaigns that work towards the prevention of smoking and passive smoking, especially in developing countries [30], where the largest number of cervical cancer deaths occurs [31].

A statistically significant association was identified only between lesion type and HIV serology (p<0.01), with a higher seropositive status for women with HSIL.

Women with HIV/AIDS have ten times greater incidence of cancer of the cervix [32] as a result of HIV-induced immuno-suppression which may facilitate the reactivation of a previous infection by HPV, producing evolution of cervical intraepithelial lesions of a higher severity and increasing susceptibility to opportunistic infections [33-35].

There was a statistically significant association (p=0.0077) between the number of sexual partners over a lifetime and the types of injuries, with the largest number of partners for women with HSIL.

The amount of previous and current sexual partners is also an important factor in HPV infection and, consequently, the risk of developing cancer of the cervix, since the greater number of partners enables greater exposure to high-risk oncogenic HPV [36-39].

Conclusion

In terms of sociodemographic characteristics, it was found that women with HPV infection were young, of reproductive age, white ethnicity, had a stable relationship, with a low level of education and no fixed income because they develop activities in the home.

Inversion of the prevalence of lesions due to age was demonstrated in this study. In women up to 39 years of age, condylomatous lesions happened more frequently, followed by HSIL and LSIL. In women aged 40 years or more, HSIL occupied first place, followed by the condylomatous lesions and LSIL, which is justified by the persistence and progression of lesions in older women compared with younger women.

It can be concluded that education and income are factors that influence access to preventive health and treatment adherence, which justifies the worst clinical findings in sociodemographically disadvantaged groups of people. On schooling, it was identified that the lower the number of years studied the greater the degree of lesions caused by HPV. While in relation to income, observing its association with the type of lesion presented, women with no fixed income were the most prevalent in all types of onset of infection.

Contrary to the initial hypothesis of this study, there was a higher frequency of women in a stable relationship in all forms of HPV infection, suggesting undue reliance on affective sexual partner and the resulting non-use of protection methods.

The use of alcohol and tobacco was associated with risk behavior for acquiring STIs. And in relation to sexual behavior, it was shown that the greater the number of sexual partners, the greater the degree of lesion presented.

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