

Diagnosis of Human Papillomavirus Infection among Heterosexual Men and Risk Factors Associated

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Abstract

Introduction: In Brazil there are prognostic of 16,340 new cases of cervical cancer for 2016. In Northeast of Brazil we have a prognosis of 5630 new cases of cervical câncer. Virtually, all cervical cancers are due to HPV infection which also accounts for 90% of anal cancers, more than 60% of certain types of oropharynx cancers and 40% of the vagina, vulva and penile cancer. In opposition to the vast amount of data related to the risk factors for acquiring the infection with human papillomavirus (HPV) in women, little is known about these factors in men.

Study Design: Was carried a observacional and cross sectional study with 83 men. These men were sexual partners of women with HPV infection. We investigate these men by peniscopy, penile citology and PCR for viral DNA search and socio- behavioral data and associations. For statistical analysis, we used the X² test with Yates' correction and multiple linear regression.

Results: Mean age was 34,6 years old, with standard deviation (SD) of 9.7 years old, peniscopy was positive in 100% of patients, the most common histological finding was koilocytosis in 76,8% of patients, the viral DNA search was positive in 14% of men and the HPV types found were 16, 31 and 33. There was a significant association between the presence of penile lesion and the time of contact with the sexual partner p = 0.020.

Conclusion: The age of the patients was similar to the literature, but the number of positive peniscopies was higher than reported. The association between penile lesion and duration of the relationship seems significant despite of other risk variables are already consolidated.

Keywords: Human Papillomavirus; Deoxyribonucleic acid; Polymerase Chain Reaction

Abbreviations

HPV: Human Papillomavirus; DNA: Deoxyribonucleic acid; SD: Standard Deviation; IARC: International Agency Research on Cancer; WHO: World Health Organization; PCR: Polymerase Chain Reaction; LCR: Long Control Region; PHRED: Phil's Read Editor; BLAST: Basic Alignment Search; STD: Sexually Transmitted Disease; CIN: Cervical Intraepithelial Neoplasia

Introduction

In Brazil there are prognostic of 16,340 new cases of cervical cancer for 2016. In Northeast of Brazil we have a prognosis of 5630 new cases of cervical cancer and in state of Sergipe is 40,3 case per 100,000 women. [1]

Virtually, all cervical cancers are due to HPV infection which also accounts for 90% of anal cancers, more than 60% of certain types of oropharynx cancers and 40% of the vagina, vulva and penile cancer [2].

Nowadays, cervical cancer is probably the best-studied prototype of a human tumor caused by a viral infection. Interactions of viral oncoproteins with cells that regulate growth are well-understood proteins, as well as the genomic modifications in cells necessary for malignant conversion related with HPV [3].

Cervical cancer tends to be diagnosed at later stages in less developed regions compared with the more developed and this combined with reduced access to appropriate facilities and medicines have an adverse effect on mortality and survival. Are expected estimates of cervical cancer to increase to 720,415 new cases and 394,905 deaths in 2025, which means an overall increase of 36% new cases and 44% of deaths [4].

In worldwide in less developed regions the International Agency for Research on Cancer (IARC) projected more than 770,000 cases of cervical cancer for 2030 and more than 432,000 deaths [5].

More than 630 million men and women were infected by HPV, according to the World Health Organization (WHO). Nine million to ten million people are infected in Brazil and 700,000 new cases are also expected each year. 105 million people are estimated to be positive for types 16 and 18 HPV in worldwide [6-8].

There are abundance of data on risk factors for acquisition of human papillomavirus (HPV) infection in women, but little is known about these factors in men. The high recurrence rate, leading to errors in judgment and complex treatments, and a strong association between HPV and cervical cancer increased even more the concern of an interest in the assessment of sexual partners of infected women [9,10].

The present study aims to determine the prevalence of penile epithelial lesions and HPV infection in male partners of women with HPV cervical lesions induced by HPV using morphological and biological methods, as well as to investigate the association between variables.

Methodology

Was carried a observacional and cross sectional study in sexual partners of women with HPV induced cervical epithelial lesions diagnosed by pathology. These patients came from the cervical pathology clinic of the federal university of Sergipe. The period of study was from June 2009 to June 2012. Were selected male and sexual partners of women patients of the Cervical Pathology office. These women had cervical epithelial injury and/or suggestion of HPV infection. These selected partners had lived with these women for a minimum period of one year. All patients signed a consent form.

In order to collect socio-behavioral data, all study subjects answered a questionnaire containing the following variables: age, origin, condom use, smoking, phimosis, hygiene, time living with a partner, extra-marital relationships, and history of STDs.

Morphological Methods

We investigate these men by peniscopy, penile citology and PCR for viral DNA search.

Was used one endocervical cell sampling brush to collect cells from pênis glans, balanopreputial sulcus, penile frenulum, penile body and urethral meatus to cytology analysis and this material was fixed on a glass slide and and this material was fixed on a glass slide and immersed in 70% alcohol and colored by the Papanicolaou method.

For cytology analysis, an endocervical cell sampling brush was used to collect cells obtained from the glans, balanopreputial sulcus, penile frenulum, penile body and urethral meatus. A cell smear of the collected material was then performed. The material was spread on a glass slide for cytology, fixed in 70% alcohol and sent to be stained by the Papanicolaou method. We used the Bethesda System 2001 cytological classification. Two different researchers reviewed twice the cytology.

To perform peniscopy a colposcope CP14 3x was used. First the researcher observe the penis with naked eye for visualization to gross lesions. Next applied 5% acetic acid in gauze and the penis was wrapped for a period of five minutes. The gauze was removed and the penis was examined with a colposcope to evaluate acetic acid positivity lesions. And after five minutes the toluidine blue solution was withdrawn with 5% acetic acid and the lesions that remained blue were biopsied.

We previously cleaned the suspected area with povidone-iodine solution and anesthetized with 1% xylocaine and biopsied. For fragment removal a 24 sized forceps biopsy was used. For cytological and histological examination, the authors considered the presence of koilocytosis as suggestive of viral infection and penile epithelial lesions were classified into grades one, two and three.

Biological Methods

To collect samples for the research of HPV-DNA, an endocervical cell sampling brush was used so that an exfoliation of glans, balanopreputial sulcus, penile frenulum, penile body and urethral meatus could be done. This material was placed in eppendorf containing 01ml of 0.9% saline solution and stored at -200 until the procedure of molecular biology was started.

Extraction and viral DNA detection

Were extracted the DNA samples of penile lesions using the Wizard® genomic DNA Purification kit, obeying the instructions recommended by the manufacturer.

Was performed in all samples na amplification of the WAF-1 gene. This gene encodes the p21 protein of the human genome. This amplification was used as endogenous control. This procedure is necessary to evaluate the quality of the extracted material. Were excluded from the study the samples that did not amplify the WAF-1 gene. We used the primers and R: 5'-GGGCGGCCAGGGTATGTAC-3'11 and F: 5'-CCCAGGGAAGGGTGTCTG-3'. The PCR reaction was performed using 50ng of genomic DNA, 20 pmol of each oligonucleotide, of each dNTP (Promega) were used 0.1 mM, (0.1% Triton X-100 50 mM KCl, 10 mM Tris HCl) 1X buffer, 1 mM MgCl₂ (Promega), and one unit of Taq DNA polymerase (Promega). The reaction for amplification was performed with a thermocycler using the following conditions: for initial denaturation of genomic material, one cycle of 94 ° C for five minutes, 30 cycles of 94 ° C for one minute, 66 ° C for 45 seconds for annealing, 72 ° C for one minute for extension and one cycle of 72 ° C for five minutes for the final extension of the fragment. Then, agarose gel stained with ethidium bromide on a 2% was analyzed with the product.

Subsequently, samples containing DNA underwent a conventional PCR protocolo to detect human papillomavirus (HPV), based on the amplification of a fragment of approximately 450bp of the L1 gene. In order, we used degenerate and consensus MY09 primers: CGTC-CMARRGGAWACTGATC and MY11: GCMCAGGGWCATAAAYAATGG .12 PCR reactions were performed in a final volume of 25µl, containing 150ng DNA, 15 pmol of each oligonucleotide, 0.1 mM of each dNTP (Promega), (0.1% Triton X-100 50 mM KCl, 10 mM Tris HCl) 1X buffer, 1 mM MgCl₂ (Promega) and one unit of Taq DNA polymerase (Promega). The amplification of the fragment of the HPV L1 gene was performed for 35 cycles at 95 ° C for 30 seconds for denaturation, 55 ° C for 40 seconds for annealing, 72 ° C for 45 seconds for extension and a cycle at 72 ° C for five minutes for the final extension. The PCR product was analyzed on 1% agarose gel stained with ethidium bromide.

Typify viral DNA

For the typifying HPV in samples of penile lesions, PCR reactions were performed using specific primers for flanking the long control region (LCR) of HPV-16, 18, 31, 33 and 58. PCR reactions were performed in a final volume of 25µl containing 100ng DNA, 20 pmol of each oligonucleotide, 0.1 mM of each dNTP (Promega), 1x buffer (50 mM KCl, 10 mM Tris HCl and 0.1% Triton X-100), 1 mM MgCl₂ (Promega) and one unit of Taq DNA polymerase (Promega). The LCR amplifications of HPV-16, 18, 31, 33, 58 were carried out in 35 cycles at 95 ° C for 30 seconds for denaturation, 55 ° C for 40 seconds for annealing, 72 ° C for two minutes for extension, and a final extension cycle at 72 ° C for 10 minutes. Then, the amplification products containing the LCR were analyzed on 1% agarose gels stained with ethidium bromide.

Sequencing DNA

Were submitted to sequencing in order to confirm the results all samples that showed HPV DNA in PCR type-specific. For purification of positive samples for HPV DNA we used the Invisorb® Fragment Cleanup (Invitek) kit, and subsequently sequenced by the dideoxy terminal fluorescent method using the ABI PRISM BigDye™ Terminator Cycle Sequencing v 3.1 kit Ready Reaction (Applied Biosystems®).

The sequencing of the samples was performed in a sequencing multiuser platform and gene expression analysis in the Central Laboratory, Federal University of Pernambuco. This was done using the automatic DNA sequencer ABI Prism 3100 (Applied Biosystems®) according to the standards established in this unit. The sequencing reactions were performed with the same set of primers used for the detection and typifying of HPV.

Analysis of the DNA sequences obtained

The quality and formation of the contig of the obtained sequences were performed by the program PHRED.13 subsequently, the obtained sequences were aligned using the Basic Local Alignment Search Tool (BLAST). After alignment, the sequences obtained were compared to reference sequences stored at GenBank. Thus, the sequencing of all samples of HPV that had a level of similarity from 98 to 100% with the sequences present in GenBank was confirmed.

Sample Size

To calculate the sample, we used the program Statcalc from Epi-Info version 7.0. Based on INCA's estimation of 220 new cases of cervical cancer in the state of Sergipe in 2012, and the fact that 50% of sexual partners of women with cervical lesions tend to have penile injury, considering an error margin of 5%, a sample of 72 subjects was obtained, with a 10% loss, obtaining a final sample of 80 subjects.

Statistical Analysis

We used the public domain software Epi Info 7 for statistical analysis. Frequency distribution tables were made. For the tests of association we used the X² test with Yates' correction and for the analysis of confounding variables a multiple linear regression was performed.

Results

Regarding peniscopy, a positivity of 100,0% was found and the most frequent finding was acetowhite lesions in 40,2% of cases.

Lesion Types	N	%
Positive acetic acid reading	33	40.2%
FPL (Flat Penile Lesion)	30	36.5%
Spiculated	8	9.7%
Positive acetic acid reading +FPL	4	4.8%
Nodule	1	1.2%
Erosion	1	1.2%
Flat and Spiculated	5	6.0%
Total	82	100.0%

Table 1: Frequency distribution of the peniscopy findings in sexual partners of women with cervical lesions HPV induced.

The cytology was negative in 42.7%, 35,4% had koilocytosis and 7.3% was diagnosed with a low-grade lesion. 14.6% the samples were inadequate. Koilocytosis was the most common histological finding suggestive of HPV infection (76,8%). 4,9% e 1,2% they were constituted of low and high grade lesions, respectively, only 2,4% were negative.

Biopsy	N	%
Condyloma	8	9.8
Low-Grade Lesion	4	4.9
High-Grade Lesion	1	1.2
Epithelial Hyperplasia	3	3.7
HPV (koilocytosis)	63	76.8
Inconclusive	1	1.2
Negative	2	2.4
Total	82	100.0
Cytology	N	%
Negatives	35	42.7
HPV (koilocytosis)	29	35.4
Low-Grade Lesion	6	7.3
Inadequate	12	14.6
Total	82	100.0

Table 2: Distribution of cytopathology and histopathology findings of penile samples of partners of women with HPV-positive cervical lesions.

There was concordance between the cytological and histological findings in 13.1% of patients without HPV. There was concordance in 33.3% (P= 0.01) of patients with HPV. There were 12 inadequate cytology and one inconclusive biopsy, which were all excluded. For statistical analysis, we used the X² test with Yates' correction as the sample had more than 40 subjects, with one cell next to five.

Penile Cytology						
Penile Biopsy	Without HPV (koilocytosis)		With HPV (koilocytosis)		Total	
	N	%	N	%	N	%
Without HPV (koilocytosis)	9	13.1	6	8.7	15	21.7
With HPV (koilocytosis)	31	44.9	23	33.3	54	78.3
Total	40	58.0	29	42.0	69	100.0

Table 3: Association between cytologic and peniscopy findings in sexual partners of women with cervical lesions.

X² with Yates correction = 0.01

For exclusion of confounding variables, we made a linear regression considering the result of the pathology in men as outcome variable. Was found a significant association between outcome variable and the time living with a partner at the expense of other variables was observed p = 0.020 and correlation r = 0.40.

Variable	P-Value
Condom	0.906102
STD	0.541706
Phimosis	0.087523
Smoking	0.999727
Penile Hygiene	0.442585
Partner's lesion	0.294993
Extra-marital relationship	0.108050
Origin	0.211224
Time with partner	0.020461

Table 4: Association between outcome of partners of women with HPV induced cervical lesions and socio-behavioral pathological risk. $R = 0.40$

To analyze the quality of extracted DNA, PCR reactions were performed with the WAF-1 gene, used as endogenous control. Out of the 104 samples analyzed (in 22 patients samples were taken twice), only 79 amplified a fragment corresponding to 290pb of the WAF-1 gene.

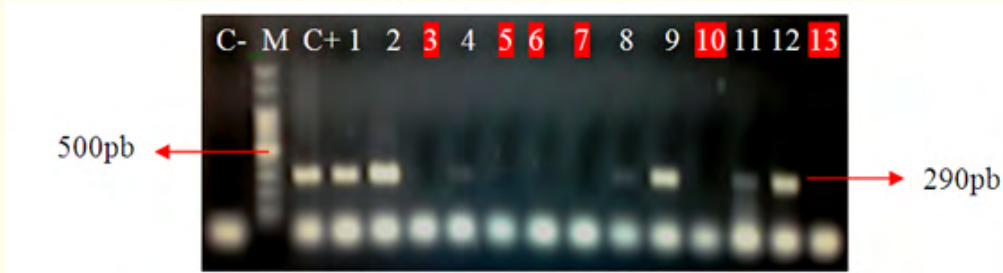


Figure 1: Representative gel of the amplification of a fragment of 290pb containing the gene WAF-1.C-

Penile lesions samples which does not present the corresponding band of LCR of HPV-16; H9: bands related to the amplification of 1000pb fragment of HPV-16 LCR; the results were visualized on 1% agarose gel after electrophoretic run at 100V.



Figure 2: Representative gel of the amplification of a 450pb fragment containing the L1 gene of HPV.

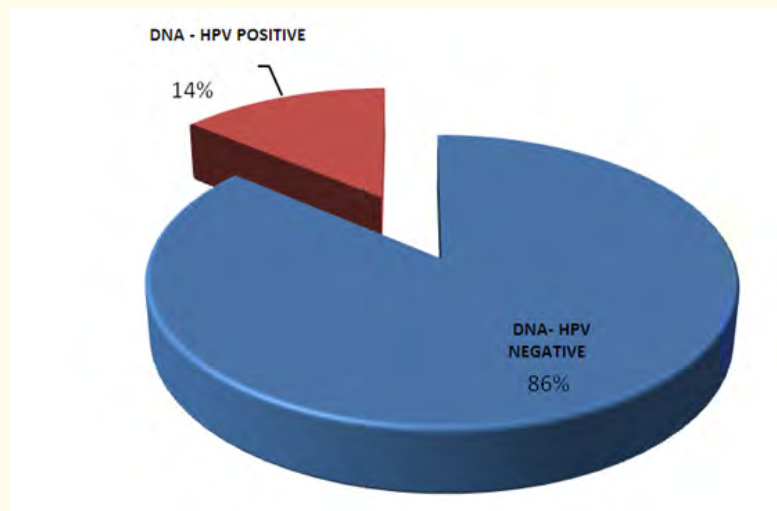


Figure 3: Percentage of infection caused by HPV in samples of penile lesions.

Discussion

All cancers and non-malignant HPV-induced diseases are necessarily preceded by HPV infection. Data about the prevalence of HPV infection and related diseases in man and in different anatomic sites is small [11].

The average age of the studied men was about 35 years, similar to the averages observed by Chaves, *et al.* (2011) [12] and by Antunes, *et al.* (2004) [9], 34.5 and 34.1 years respectively.

Patients reported constant condom use in 74.3% of cases. In accordance to the results of a multicenter study done with men in Brazil, Mexico and the United States, some type of HPV was found in 65.9% of men who always used condom and in 71.9% of men who did not always wore condom [14]. Rombaldi, *et al.* (2006) [14] found 57% of men with HPV DNA-positive who had never used condom with their regular sexual partners and neither with sex workers and 51.4% used condom regularly in such situations, unlike the findings observed in the research.

According to Chaves, *et al.* (2011) [12], history of STDs was not associated with HPV infection. In our study, the presence of STD was positive in 17.1% of men, with gonorrhea being the most frequent in 64.4% of patients. Gonorrhea was also the most common STD in studies conducted by Rombaldi, *et al.* (2006) [14] and Hippelainen, *et al.* (1991) [15]. Nicolau, *et al.* (2005) [16] found 22.4% of history of STDs in sexual partners of women who had cervical lesion.

Men denied having phimosis in 90,2% of the cases. However, none of those who denied phimosis reported having been circumcised. Presence of phimosis, was quantified from the interview and not observation during the examination, probably have generated an information bias. Bleeker, *et al.* (2005) [17] found in their study the absence of circumcision among 95.8% of the sexual partners of women with cervical intraepithelial neoplasia (CIN). Chaux, *et al.* (2013) [18] observed the presence of 57% of patients with phimosis and penile cancer in their study. Literature data shows that high-risk HPVs types are more common in uncircumcised men [19].

Dunne, *et al.* (2006) [20], in a systematic review, linked circumcision with a statistically significant reduced risk for acquiring HPV. Miralles-Guri, *et al.* (2009) [21], in a systematic review study, concluded that the variation in the incidence of penile cancer in the world could be explained by variation in the number of sexual partners and circumcision rates.

Although only 8.6% of men referred to be smokers, this data doesn't differ from the one found by Franceschi, *et al.* (2002) [22], who performed a multicenter study analyzing sexual partners of women with CIN and cervical cancer, finding only 15% of smokers without significant association with the presence of HPV. Data corroborated by Frega, *et al.* (2006) [23] who also found no statistical significance between the partners infected with HPV and smoking. However, Teixeira, *et al.* (1999) [24] found a significant association between smoking and HPV infection in 44.9% of the sexual partners.

Penis hygiene was found inadequate in 7.4% of cases. Chaux, *et al.* (2013) [18] found 90% of the association between poor hygiene and penile cancer.

Most patients reported not having had extramarital affair in the last year, representing 51.2%, a result close to the one Nicolau, *et al.* (2005) [16] found which showed that 60% of the sexual partners of women with cervical lesion were not involved in extramarital affairs. In a study evaluating behavioral risk factors in 1.545 men, 22.6% of patients were positive for high-risk HPV, and among these patients there was reference to more than two sexual partners in a year [25].

The most frequent injury found in women was low grade in 50% of cases. Teixeira, *et al.* (1999) [24] found the prevalence of low-grade lesion in 30.1% of partners of men with HPV infection. Frega, *et al.* (2006) [23] found a 87.1% prevalence of low-grade lesion among the partners of their patients.

Most men, 51.2%, denied having had extramarital affair in the past year. Franceschi and colleagues (2002) [22], in a study conducted by the International Agency for Research on Cancer (IARC), found a prevalence of 13.3% of HPV infection in men with one partner, while 59.5% had no HPV infection. In their study, a meta-analysis was performed to assess the association between HPV infection and the number of sexual partners in different countries and no statistical significance was found for this association. In our study, through linear regression, we observed that there was no significant association between the variable number of extramarital relations and the presence of penile epithelial injury or HPV infection in men.

Considering the result of the pathology as an outcome variable, we performed a multivariate linear regression noting the significant association between the time spent together with the sexual partner over other epidemiological variables and risk factors already consolidated. This is perhaps the most important finding of this study, as the literature mentions strong evidence of the number of partners as a risk factor and little is reported regarding relationship time. Man is an important source for HPV transmission, but is also the target of infection and epithelial injury due to prolonged sexual intercourse with the infected partner. The study of the association between marital stability ≥ 6 years revealed the presence of HPV DNA in 60.7% of married men [14].

In a British study conducted between 1999 and 2001 to assess risk factors involved in the transmission of HPV infection among men and women through a bivariate analysis, we observed a strong association between high-risk HPVs and the following factors evaluated in men: number partners throughout life, partners in the past year, concurrency of sexual partners, smoking and alcohol consumption, age at first sexual intercourse [25]. In the present study, however, we observed a different behavior in the studied population, where the time spent together with carrier partner of epithelial injury was more significant than the number of sexual partners for the acquisition of penile lesions.

There was a prevalence of a 100% positivity of the peniscopy. Studies show that when stable sexual partners of women infected with HPV are observed through peniscopy, 30 to 65% injury present penile lesion [14,26-28].

However, it should be noted false-positive results associated with a higher inflammatory response [30]. In a study conducted with 270 male partners of women with HPV infection, positivity in peniscopy was found in 100% of patients, with a total of 311 biopsies being performed; but pathology results, 81 (26%), were not considered suspected [16]. In our study, we found only one negative pathology result and two inconclusive ones. We found a very high prevalence of positive peniscopy that could represent a bias due to false positives

induced by inflammatory changes, but when the findings in the peniscopy were compared with the pathology findings, we found only three unchanged exams, representing 3.6%.

Regarding the types of injuries found on peniscopy, there was a higher prevalence for positive acetic acid reading lesions (40.2%), followed by the finding of Flat Penile Lesion (36.5%). Bleeker, *et al.* (2002) [31] found in 69% of all peniscopies done in the sexual partners of women who had CIN the Flat Penile Lesion. Costa, *et al.* (1992) [31] found a frequency of 75.4% of injuries that were positive for acetic acid. The Flat Penile Lesions are papular epithelial lesions on the penile that present important viral load of high risk HPV. There was a lower prevalence of Flat Penile Lesion compared to the literature, there was a higher prevalence of lesions positive for acetic acid. There was, perhaps an observational bias and some lesions could be Flat Penile Lesions and classified as positive for acetic acid.

Among the pathology results a higher prevalence of koilocytosis findings was observed, suggestive of HPV infection (76.8%) and low-grade penile lesions 4.9%. Antunes, *et al.* (2004) [9] observed 77.3% of biopsies with koilocytosis in their findings suggestive of HPV infection. But Teixeira, *et al.* (1999) [24] found 43.8% of sexual partners of women with high-grade cervical intraepithelial neoplasia and 30.1% of partners of women with low-grade squamous intraepithelial lesion positive for the presence of koilocytes in 73 % of cases, suggesting viral infection.

Our findings of 4.9% of low-grade penile injury are superior to what is reported in the literature where some studies found a prevalence of between 1 and 3% in the pathology findings. 17,29,30 Bleeker, *et al.* (2002) [30] found 28% in their pathological findings and Hippelainen, *et al.* (1994) [15] found 7% in their study.

Cytology showed abnormalities suggestive of HPV infection (koilocytosis) in 35.4% of patients. The negative cytology totaled 42.7%. Twelve cytology (14.6%) were considered inadequate. Frega, *et al.* (2006) [23] found 6% of cytological abnormalities suggestive of HPV infection and Hippelainen and colleagues (1994) [15] found 9% of cytology suggestive of viral infection, all these values were lower than our findings. González, *et al.* (1991) [32] found 30% positivity which was closer to our findings. The number of inadequate smear tests can be attributed to the difficulty of exfoliation and to get adequate fixation of the cells of the penis during the usual cytological collection. We found a prevalence of 7.3% of low-grade lesions, values which exceed the pathological findings. We believe that these findings might be due to careful observation of glass slides performed by two authors, each glass slide twice reviewed and by that increasing the accuracy of this method, even using the conventional technique.

A significant association between cytological and histological findings ($p = 0.0134$) was found, showing 33.3% concordance of the koilocytosis findings and 13.1% concordance of the negative findings. Teixeira, *et al.* (1999) [24] found an association of 99.3% between negative cytology and negative biopsies of the penis for changes suggestive of HPV infection. González, *et al.* (1991) [32] examining 113 partners of women with CIN and condylomas, observed that the cytology and biopsy were concordant in 30.8% of cases and discordant in 46%. Although cytology is not a recommended method for tracking penile epithelial lesions and abnormalities suggestive of penile HPV infection, it shows itself as an adjuvant to be considered in the investigation of these changes.

We found only 14% of the samples with the presence of HPV DNA. We attribute this decreased percentage to the loss of genomic material because of collecting difficulty through exfoliation. The results obtained using type-specific PCR showed presence of HPV types 16, 33 and 31 in the samples and the two co-infection, 16 and 31, 16 and 33. This is the first study conducted in this particular population. And we were able to demonstrate the typing of HPV present in samples of material obtained from the penis. In a study with partners of women with cervical lesions found a prevalence of 31% for high-risk HPV and 4% prevalence for low-risk HPV in a total of 35% of positivity for HPV in samples collected by exfoliation [34]. Rombaldi, *et al.* (2006) [14] found positivity for HPV in 55% of their samples through exfoliation and biopsy. Parada, *et al.* (2010) [34] examining 504 couples in Mexico found a positivity for HPV in 20.4% of men.

Dunne., *et al.* (2006) [20] reviewing 40 publications on HPV infection in men, reported the prevalence of HPV infection from 1.3% to 73%. Most studies have reported a prevalence of over 20% depending on the studied population, sampling sites and processing methods.

Conclusion

Among the morphological findings peniscopy showed a very expressive positivity above from the one found in the literature.

The most prevalent lesions found in peniscopy were positive for acetic acid, followed by flat penile lesions.

The majority of the patients had around 35 years old, came from the countryside, denied phimosis and history of STDs, they used condoms, had a non-smoking habit and performed an adequate penile hygiene, denied extramarital relationships and had a relationship time of more than five years with their partners.

The most common injury to the sexual partner was of low-grade.

There was a significant association between the presence of penile epithelial injury and the time of living with their partners at the expense of other risk factors.

A significant association between histological and cytological findings was found.

The PCR showed a low positivity for the presence of HPV DNA.

HPVs' types found were 16, 31 and 33 with the presence of co-infections.

Conflict of Interest

The authors declare that they have no personal or financial relationship(s) which may have inappropriately influenced them in writing this manuscript.

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