INTRODUCTION

Infection with HPV is the most frequent sexually transmitted disease (STD) in the world. The World Health Organization (WHO) estimates around 630 million new cases per year, and 30 million of these are associated with Condyloma acuminatum, 30 million with low-grade lesions, 10 million with high-grade lesions, and 500 thousand with cervical cancer. The development of these lesions is directly related to the presence of different HPV types (1).

Cervical cancer is the most common death cause of adult women in developing countries, and the second more common cancer in women worldwide (3), with an estimate of half a million new cases and 274,000 deaths/year, according to WHO (2). In Brazil, the estimate for 2010 was 19,603 new cases and 8,286 deaths resulting from the disease (3). Immunosuppression, mainly acquired, is the major cause of the manifestation of HPV infection. Currently, the HIV infection is considered a pandemic problem, especially in developing countries. This disease has increased the prevalence of HPV infection, increasing the risk to cervical neoplasia. In 1993, invasive cervical cancer was added to the list of defining diseases of Acquired Immunodeficiency Syndrome (AIDS) by the Centers for Disease Control and Prevention (CDC) in the USA (4). The role of HPV in the genesis of cervical cancer is biologically and epidemiologically well established (3), although HPV aetiological contribution to co-infection in the genesis of cervical cancer remains uncertain (6).

Studies have shown that HIV positive women have a higher prevalence of infection with HPV (6-13), and these women are often infected with a greater number of types of viruses than the HIV negative women (5). The presence of multiple viral types (3) and viral types of high oncogenic risk (14) is related to adverse outcomes, such as persistent infection, and increase of both prevalence and lesion progression. In addition, there is evidence of a greater prevalence of intraepithelial neoplasia among HIV positive women when compared with the HIV negative women (6,12,13).

In general, the prevalence of HPV increases with progressive reduction of CD4 cells (6,12,13) and the presence of multiple types can also increase with the progressive CD4 (12) reduction. Furthermore, the infection with this virus is also more persistent in the HIV positive population (6,12,13), which can contribute to its greater prevalence and also to a higher risk of cervical epithelial lesions. Some factors have been associated with the progression of these lesions, such as the prolonged use of hormonal contraceptives (more than 10 years), multiparity, smoking, co-infection with other STD (such as HIV itself, herpes simplex 2, and Chlamydia trachomatis), and immunosuppression (3).

However, it is unclear if HIV infection increases the susceptibility to a genital HPV infection, no matter the epidemiological risk patterns, or if it modifies the associations with specific types of HPV and the cervical disease documented in general population (6). It is also important to remember that factors related to HPV-HIV co-infection, such as viral types, variation in the immune status, and presence of citopathological changes, when crossed with different populations, show conflicting results, revealing the importance of regional, ethnic, and demographic characteristics, and also studies planning.

OBJECTIVE

Compare the positivity of HPV genital infection in both HIV positive and negative women, evaluating the prevalence of high-
risk and low-risk viral types among the groups, as well as the relation with socioeconomic, demographic, and behavioural factors, in addition to variables related to HIV infection, such as CD4 cells level, viral load (VL), and use of Highly Active Anti-Retroviral Therapy (HAART).

**METHODS**

This is an observational and transversal study, performed in the city of Florianópolis, state of Santa Catarina, Brazil, from December, 2007, to April, 2010. The samples size calculation was based on the Brazilian study by Campos et al.\(^\text{(16)}\), which found HPV DNA prevalence of 73% among women HIV infected, and 24% among HIV negative women.

Considering a statistics power of 80%, a significance level of 5% (p < 0.05), and a 1:1 case-control relation, it was observed that a sample of 38 women (19 HIV positive and 19 HIV negative women) would be enough for this study. Therefore, two samples were selected: the first one was composed of 20 HIV positive women of the Hospital Nereu Ramos (HNR), specialized in infectious diseases hospital; the second sample consisted of 99 HIV negative women of the gynecology clinic at the University Hospital Polydoro Ernani de São Thiago. All subjects of this study have searched for the infectious disease or gynecology services for regular appointments or complaints not related to a possible sexually transmitted disease. All women infected with HPV before starting the study were excluded.

All volunteers who have agreed to participate of this study have read, discussed with investigator and signed the Consent Term, for interview and records, and to collect genital samples. Collection of samples (endocervical and ectocervical region) for HPV DNA detection and its oncogenic risk was performed using the Female Swab Specimen Collection Kit™ (Digene Corporation). Samples were obtained from endocervix (with 360° rotation movements) and ectocervix as well, using the same swab. They were then stored in specific means of transport (Sodium azide 0.05%, 1 mL), properly identified (identification number and initials) and frozen. These Samples were submitted to a molecular biology study by Digene & Co. Hybrid Capture Method II™, in the Dnanálise laboratory, in Florianópolis, for the HPV DNA detection. This method has a clinic sensitivity of 1 pg/mL, equivalent to 0.1 copy of virus per cell, and can detect 70% of low-risk HPV types (6, 11, 42, 43, and 44) and 99% of high oncogenic risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 60).

The test was considered positive when RLU (Relative Light Units) ratio of two positive controls was equal to 1 pg/mL of HPV DNA or more. According to recent studies, this cutting point value adds greater sensitivity and specificity to the examine\(^\text{(15)}\). After, registered data were collected and charts filled up with the interview with patients, such as schooling level, race, parity, tobacco smoking, oral contraceptives (OC) use, and antiretroviral therapy. The obtained data were stored in a database EpiData® software, version 3.1, and the statistical analysis carried out by SPSS®, version 17.0, and StatCalc® software programs. A case-control type analysis was performed, where cases were represented by 20 HIV positive women, and controls by 99 HIV negative women. The measure of frequency used was the prevalence, while the measures of association were the ratio of prevalence, the Chi-square (X²), and the Fisher exact test, with a confidence interval of 95%. The result was considered significant if the error probability was ≤ 5% (p < 0.05). The current procedures are in accordance with the ethical principles set out by the National Commission of Ethics in Research and approved by the Ethics Committee in Research with Human Beings from UFSC. This study has been approved by this Committee under registry 325/2007 and 330/2009.

**RESULTS**

Infection with HPV (HPV DNA) was found in 70% of HIV positive women, while in HIV negative women the infection was present in 21.2% (p < 0.001), with a ratio of prevalence of 3.3 (IC 95%; [2.05-5.3]), as shown in Table 1. High oncongenic risk HPV was found in 71.4% of HIV positive women, while the low oncogenic risk were found in 64.3%. Both types were concomitantly found in 35.7% of HIV positive women, and in 23.8% of HIV negative women. The high-risk HPV was observed in 71.4% of HIV negative patients (Table 2).

The average age of HIV positive women group was 44.7 years old (varying from 28 to 56 years old), and in the control group was of 36.3 years old (varying from 17 to 63 years old). In the HIV positive women group, HPV was significantly more frequent in women over 35 years old (78.5%). In control group, the prevalence of HPV infection was also more frequent over 35 year old women (42.8%), however, it was distributed in a more uniform way (Table 3).

With regard to schooling, most HIV positive women infected with HPV had only elementary school (57.1%), while in the HIV negative women the same percentage (57.1%) was observed on women with high school graduation. Among women with elementary school graduation, the prevalence for HPV DNA was significantly greater (72.7%) among HIV positive women than in the control group (23.5%). Those who attended high school and college showed a HPV DNA greater prevalence in HIV positive women, but not significantly (Table 3).

In relation to ethnicity, HPV DNA prevalence was higher among white HIV positive women group (92.8%), and also in white HIV negative women (85.7%). With regard to parity, the HPV DNA was more common in nulliparous women of both groups (85.7% HPV positive, and 66.6% negative). HPV infection was more common in non-smokers of both groups (64.2% HIV positive, and 76.1% HPV negative). In the HIV positive group, HPV was more common in oral contraceptive non-users (85.7%), while in the control group it was more frequent in OC users (76.1%) with statistical evidence of association (Table 4).

<table>
<thead>
<tr>
<th>HIV</th>
<th>HPV (+) (n = 35)</th>
<th>RR</th>
<th>95% IC</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>14</td>
<td>70.0</td>
<td></td>
<td>0.000012</td>
</tr>
<tr>
<td>Negative</td>
<td>21</td>
<td>21.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Chi-square test.
† Percentage of groups’ total women.
significance. **Table 3** describes the prevalence of HPV per category among both HIV positive and negative women in relation to the discussed variables.

When we analyse the group of women infected with HIV, we verified that most HPV positive cases were found in those with CD4 cell levels > 500 cells/mm³ (57.1%), however, among women with CD4 < 200 cells/mm³, all were positive for HPV infection (100%). When we compared the HPV infection between groups, a significant association with this infection was observed for women with CD4 cells counting between 200 and 500 cells/mm³. Among women with undetectable viral load, 66.6% were HPV DNA positive.

The remaining HIV positive women showed variable viral loads (between 840 and 42,373), and only one of them did not present HPV, totalling a prevalence of 80%. Among women receiving HAART, the HPV DNA prevalence was 87.5%. The HPV DNA was negative among all women who were not in use of HAART, which were a statistically significant difference (**Table 4**).

**DISCUSSION**

It was found a significantly higher prevalence of HPV infection (HPV DNA) in HIV positive women (70%) when we compare with the HIV negative women (21.2%). This difference represents a 3.3 times higher risk for the HIV positive women. World data demonstrate different results for HPV prevalence among these groups. However, the tendency to a greater prevalence among HIV positive groups is invariably observed.

In Sun et al. study, HPV DNA was found in 60% of HIV positive women, while among the HIV negative women the prevalence was 36%. Minkoff et al. found a prevalence of 73% versus 43%, respectively.

A meta-analysis that included important studies about HIV infection showed a prevalence of 64% versus 28% in HERS (HIV Epidemiology Research Study, 1999) study, and 63% versus 30% in WHIS (Women’s Intergency HIV Study, 1999) study for both HIV positive and negative women, respectively. Brazilian studies, however, such as Campos et al., found significant differences between both groups, showing a HPV DNA prevalence in 73.2% of HIV infected women, and 23.7% among HIV negative women, a result very similar to our study.

Nevertheless, Levi et al. showed 87% of HIV positive women and 100% of HIV negative women positive to HPV DNA. In this study, control group women were selected in a cervical pathology clinic, and a high positivity was expected to HPV DNA.

The investigators of a study from the specific region of Brazil (state of Bahia) found a prevalence of 100% of HPV DNA among HIV positive women, predominantly in Afro-descendants’ individuals. Similarly, a prevalence of 98% for HPV was found in a study using the polymerase chain reaction (PCR), which included only HIV positive women in São Paulo. However, another study of the same authors using the hybrid capture method showed the HPV prevalence of 64.5% among positive HIV women.

**DISCUSSION**

It was found a significantly higher prevalence of HPV infection (HPV DNA) in HIV positive women (70%) when we compare with the HIV negative women (21.2%). This difference represents a 3.3 times higher risk for the HIV positive women. World data demonstrate different results for HPV prevalence among these groups. However, the tendency to a greater prevalence among HIV positive groups is invariably observed.

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**Table 4** – Prevalence of HPV in relation to CD4 cells counting, viral load (VL), and use of HAART among HIV positive women.

<table>
<thead>
<tr>
<th>Variables</th>
<th>HIV (+)</th>
<th>HIV (-)</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n %*</td>
<td>n %*</td>
<td></td>
</tr>
<tr>
<td><strong>CD4 (cell/mm³)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 200</td>
<td>03 100.0 – –</td>
<td>0.319298</td>
<td></td>
</tr>
<tr>
<td>200-500</td>
<td>03 37.5 05 62.5</td>
<td>0.018059</td>
<td></td>
</tr>
<tr>
<td>&gt; 500</td>
<td>08 88.9 01 11.1</td>
<td>0.119195</td>
<td></td>
</tr>
<tr>
<td><strong>VL (copies/mL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable</td>
<td>10 66.6 5 33.4</td>
<td>0.516511</td>
<td></td>
</tr>
<tr>
<td>Detectable</td>
<td>04 80.0 1 20.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HAART</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14 87.5 2 12.5</td>
<td>0.003096</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>– – 4 100.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Percentage of groups’ total women.
† Fisher’s test.
A possível razão para o aumento na prevalência de infecção pelo HPV em mulheres HIV positivas poderia ser explicada pelo mecanismo de infeção: um sistema imunológico que falha ao controlar a infecção do HPV, aumentando a taxa persistente e detetada. A replicação viral pode ser mais eficiente em indivíduos com comprometimento imunológico, contribuindo para taxas mais altas de infeção viral persistente e detetada. O design diferente das pesquisas e a utilização de diferentes técnicas de identificação de DNA viral podem contribuir para a variação na prevalência encontrada em várias pesquisas. No entanto, a prevalência de HPV positiva em mulheres HIV positivas é observada independentemente do teste realizado.

Os resultados das nossas observações mostraram um alto nível de prevalência de alto risco de tipos virais em ambos os grupos (71.4%), juntamente com um maior nível de prevalência de ambos os tipos de HPV em mulheres HIV positivas, com 35.7% versus 23.8% em mulheres HIV negativas.

Em vários estudos, a infecção múltipla foi prevalente entre mulheres HIV positivas e negativas, e a prevalência de infeção viral de alto risco foi significativamente aumentada (19,21), revelando uma correlação com os dados encontrados neste estudo. Uma infeção com vírus de baixo risco também foi observada entre mulheres HIV positivas, reforçando a tendência para uma prevalência mais alta de HPV em mulheres HIV positivas, independentemente do tipo.

Alguns estudos verificaram que mulheres jovens expostas a um risco de infecção com HPV e HIV têm uma prevalência mais alta, com uma importante declínio após os 25-30 anos de idade (1,21). Neste estudo, um aumento da prevalência de HPV em mulheres entre 35 e 39 anos foi observado em ambos os grupos e, significativamente, em mulheres HIV positivas (78.5%) em comparação com mulheres HIV negativas (42.8%). Outros estudos (1,19,21) mostraram que outra prevalência de HPV, com um segundo pico no pós-menopausa de idade (mais de 50 anos), ocorre apenas em algumas regiões estudadas. Neste novo padrão, bimodal, é explicado por um aumento da resposta imune por alterações hormonais menopausáticas que podem reativear infecções latentes (19-21), e também aumentar a vulnerabilidade ao HPV. O segundo mecanismo teria como base o comportamento sexual das mulheres, resultando em novas infecções com o vírus (21).

As prevalências de HPV foram encontradas entre mulheres HIV positivas que receberam apenas uma educação primária (72.7%), bem como no aqueles que frequentaram uma escola secundária (62.5%). Os resultados concordam com a expectativa de uma prevalência maior em classes socioeconômicas inferiores. De acordo com a meta-análise envolvendo estudos de todas as continentes (exceto Oceanía), a prevalência de HPV foi mais alta em países em desenvolvimento (15.5%) do que em países desenvolvidos (10%) (19). Cavalcanti et al. (22), em um estudo brasileiro de amostras de população em geral, encontraram um predomínio de 10.7% entre mulheres de classe socioeconômica mais baixa (classes privadas do serviço, etc.), ao passo que entre mulheres de status socioeconômico mais alto (classes privadas do serviço, etc.) a prevalência foi de 31.1%. O risco de infecção por HPV aumentou 1.72 vezes nesse grupo. Uma associação significativa entre infecção viral e infeção pelo HPV foi observada em mulheres com alto status socioeconômico que frequentaram uma escola secundária, evidenciando um efeito sinérgico entre HPV e HIV.

Alguns estudos mostraram um maior risco de infecção por HPV em mulheres negras e mulheres descendentes, bem como uma associação entre a prevalência de câncer cervical e a multiplicidade de infecção, fumo (24-26) e uso de contraceptivos orais (5,20,27). Em alguns dos estudos, essas variáveis não estavam relacionadas com a presença de HPV na mulher HIV positiva.

Na pesquisa de Palefsky et al. (28), uma análise de prevalência e progressão de HPV foi realizada, com resultados consistentes com os dados existentes. Statkins et al. (29) verificaram um significativo aumento entre HPV e CD4 > 200 células/mm³, OR = 1.9. Observamos uma prevalência mais alta de infecção por HPV em mulheres CD4 < 500 células/mm³. Em nosso estudo, a prevalência de infecção por HPV foi mais alta para mulheres HIV positivas com infecção viral não detetada, e mais baixa em mulheres com infecção viral detetada.

Estudos mostraram resultados controversos sobre a prevalência e progressão de HPV em mulheres combinadas com uso antiretroviral. Neste estudo, observamos que a prevalência de infecção por HPV foi maior em mulheres HIV positivas que utilizaram antiretrovirais, sugerindo uma correlação com uma maior prevenção de infecção por HPV entre mulheres HIV positivas que utilizaram antiretrovirais.

Observamos que a prevalência de infecção por HPV em mulheres HIV positivas é significativamente mais alta do que na população HIV negativa, e as infeções de alto risco por HPV são as mais comuns. A prevalência de infecção por HPV em mulheres HIV positivas com age 35 anos com somente uma educação primária, bem como a menopausa, aumentou o risco de infecção por HPV. A prevalência de infecção por HPV aumentou em mulheres que tinham usado antiretrovirais.

Assim, novas pesquisas são necessárias para melhor entender a associação entre essas duas infeções. As pesquisas de larga escala sugerem que a prevalência de infecção por HPV em mulheres HIV positivas é significativamente mais alta do que na população HIV negativa, e as infeções de alto risco por HPV são as mais comuns. A prevalência de infecção por HPV em mulheres HIV positivas com age 35 anos com somente uma educação primária, bem como a menopausa, aumentou o risco de infecção por HPV. A prevalência de infecção por HPV aumentou em mulheres que tinham usado antiretrovirais.

CONCLUSÃO

A prevalência de infecção por HPV foi 3,3 vezes maior em mulheres HIV positivas (70%) do que em mulheres HIV negativas (21,2%), e na maioria destes casos, o risco de infecção por HPV foi significativamente maior.

Conflito de interesses

Os autores declaram nenhum conflito de interesse.

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