

Human papillomavirus infection and risk factors to cervical cancer in asymptomatic women in the region of the Northeast of Brazil

Infecção pelo papillomavirus humano e fatores de risco para o cancer cervical em mulheres assintomáticas em uma região do Nordeste do Brasil

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Abstract

Objective: This study sought to identify the presence of HPV infection and the risk factors related to susceptibility to cervical cancer in asymptomatic women. **Methods:** It is a cross-sectional study with 428 users attended Basic Health Units, in Arapiraca, Alagoas, Brazil. Sociodemographic, behavioral variables, and cytopathological reports were collected. Molecular detection of the HPV virus was performed by Nested-PCR. Statistical analysis was conducted with SPSS version 22.0. **Results:** A total of 428 women were studied, HPV DNA detected in 39.2% (n = 168), with a mean age of 41 years old. There was an association of HPV with use of oral contraceptives (p <0.016) and alcoholism (p <0.038). It was showed a higher frequency of positive HPV in women older than 25 years old (88.7%), up to 5 sexual partners (93.4%), up to 3 pregnancies (71.4%), and with the cytopathologic results within the limits of normality (61.9%). HPV was identified in 40.3% (104/258) of the women with results within the limits of normality. **Conclusion:** Our results suggest that the use of oral contraceptives and alcoholism may be considered as possible risk factors related to cervical oncogenesis. With this, it is necessary to propose interventions aimed at the health education of this population, actions of prevention, and early detection.

Keywords: Papillomaviridae. Women's Health. Pap Smear. Cervical Neoplasms.

Resumo

Objetivo: Este estudo buscou identificar a presença de infecção pelo HPV e os fatores de risco relacionados à suscetibilidade ao câncer do colo do útero em mulheres assintomáticas. **Métodos:** Trata-se de um estudo transversal com 428 usuários atendidos em Unidades Básicas de Saúde, em Arapiraca, Alagoas, Brasil. Foram coletados relatórios sociodemográficos, variáveis comportamentais e citopatológicos. A detecção molecular do vírus HPV foi realizada por Nested-PCR. A análise estatística foi realizada com SPSS versão 22.0. **Resultados:** Foram estudadas 428 mulheres, com DNA de HPV detectado em 39,2% (n=168), com média de idade de 41 anos. Houve associação do HPV com o uso de anticoncepcional oral (p<0,016) e alcoolismo (p <0,038). Foi evidenciada maior frequência de HPV positivo em mulheres maiores de 25 anos (88,7%), até cinco parceiros sexuais (93,4%), até três gestações (71,4%) e com resultados citopatológicos dentro dos limites da normalidade (61,9%). O HPV foi identificado em 40,3% (104/258) das mulheres com resultados dentro dos limites da normalidade. **Conclusão:** Nossos resultados sugerem que o uso de anticoncepcionais orais e o alcoolismo podem ser considerados como possíveis fatores de risco relacionados à oncogênese cervical. Com isso, é necessário propor intervenções voltadas para a educação em saúde dessa população, ações de prevenção e detecção precoce.

Palavras-chave: Papillomaviridae. Saúde da Mulher. Papanicolau. Neoplasias cervicais.

INTRODUÇÃO

Human papillomavirus (HPV) infection is the main risk factor for the development of cervical cancer. It is estimated that 80% of people who have an active sex life will be infected at some point in their life, once or multiple times¹. This virus infects the human epithelium, often transiently, and may regress between one and two years after exposure^{1,2}.

Risk factors associated with persistent infection by some type of

oncogenic HPV can lead to the development of pre-cancerous lesions that if identified and treated properly, prevent progression to cervical cancer³. There are more than 200 types of HPV recognized⁴, where at least 13 are considered oncogenic and associated with precursor lesions of cervical cancer, while the others are related to genital and cutaneous warts⁵. Cervical cancer is one of the most common cancers in the world. In 2012, 527 thousand new cases were estimated. On the world

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stage is the fourth most common cancer among women. In Latin America, it represents the second most incident and the second cause of death⁶.

In Brazil, according to estimates by the National Cancer Institute for the 2016/2017 biennium, 16,340 new cases of cervical cancer are expected, ranking the third position among the most common cancers in the female population and the fourth cause of death of women for cancer⁷. The scenario of this pathology by region remains worrying, where the incidence, without considering non-melanoma skin tumors, in the Northern Region (23.97 / 100 thousand) is the largest in the country. The Central-West (20.72 / 100 thousand) and Northeast (19.49 / 100 thousand) regions continue to occupy second place; the Southeast Region (11.30 / 100 thousand) the third; and the South Region (15.17 / 100 thousand), the fourth position⁷.

In addition to human Papillomavirus infection, other factors are related to the development of cervical cancer, such as immunological conditions, genetic conditions, sexual behavior², age, smoking, early sexual initiation, the multiplicity of sexual partners, multiparity, and use of oral contraceptives⁸. Considering this context, it is realized that HPV infection is a necessary factor, which is associated with other factors that can develop this neoplasia (9). In this way, detecting the presence of HPV infection and the associated risk factors for cervical cancer susceptibility can provide women targeted clinical practice and prevention of these diseases. Thus, the objective of this study was to identify the presence of HPV infection and the risk factors related to susceptibility to cervical cancer in asymptomatic women in a region of the Brazilian Northeast.

METHODS

The project was approved by the Ethics and Research Committee of the Federal University of Alagoas under opinion 931.700 and Certificate of Presentation for Ethical Appreciation (CAAE) under registration 31450014.9.0000.5013.

Subjects

This is a descriptive and cross-sectional quantitative study performed with 428 users during the gynecological nursing consultation in Basic Family Health Units, in the city of Arapiraca, Alagoas, Brazil, between November 2014 and December 2015. The study population was composed of women selected according to the following criteria: search for oncologic colpocytology, who initiated sexual life, over 18 years of age, who were not pregnant or menstrual period, and who agreed to participate in the research and signed the Free and Informed Consent Term. The following exclusion criteria were adopted: non-continuity of the patient during the gynecological visit, hysterectomized, under 18 years and who did not accept to participate in the study. The instrument used for data collection was a semi-structured questionnaire with sociodemographic characteristics, sexual history, reproductive history, clinical

history, smoking habits, and alcoholism.

The cytopathological reports were obtained from the Cervical Cancer Information System (SISCOLO), which assists the National Cancer Control Program and the Viva Mulher Program. They were classified according to the Bethesda Nomenclature in their last review, which details the descriptive nomenclature of the findings of gynecological cytology⁹. In the study were considered normal results those who had in their description: within the limits of normality and as altered those with benign alterations or abnormalities of epithelial cells.

Molecular detection of HPV

The biological material collected consisted of a sample of epithelial cells from the ectocervix and endocervix for oncotic colpocytology and for molecular diagnosis of endocervix cells. The samples were processed for DNA extraction using the PROMEGA commercial kit. For internal control of the reaction, PCR amplification was performed with primers specific for the human β -actin gene using the forward primer 5'-AGCGGGAAATCGTGCGTG-3' and the reverse primer 5'-GGTGATGACCTGGCCGTC-3' that amplifies a region with a 134 bp fragment. The conditions for PCR were denaturation at 95 ° C for 2 minutes; denaturation in 40 cycles at 95 ° C for 1 minute, 60 ° C for 1 minute, annealing at 72 ° C for 1 minute; extension at 72 ° C for 5 minutes. In the negative controls, ultrapure water was used.

HPV detection was performed in two steps. The first was by PCR using primers MY09 / MY11 5'CGTCCMAARGGAWACTGATC3' and 5'GCMCAGGGWCATAAYAATGG3', which amplifies a fragment of 450 bp. The product of this reaction was used for the second step using nested-PCR technique and GP5 + / GP6 + 5'TTTGTTACTCTGGTAGATAC3' and 5'GAAAAATAAAGTAAATCA3', amplifying a 150 bp fragment, both of the L1 region. The PCR reaction product was visualized on 2% agarose gel stained with ethidium bromide and subsequently photographed by the L.Pix Transilluminator apparatus (Loccus Biotechnology).

Statistical analysis

The database, including sociodemographic and behavioral factors, was analyzed using the Statistical Package for Social Sciences (SPSS) software version 22.0. The variables analyzed were: ethnicity, age, marital status, schooling, family income, age of first sexual intercourse, number of partners, number of pregnancies, período of the last preventive exam, current contraceptive method, history of Sexually Transmitted Infection (STI), smoking and alcohol habits. The descriptive analysis presented the frequency distributions, calculation of mean statistics, and standard deviation. Odds ratios (OR) with a 95% confidence interval (95% CI) were calculated and the Fisher exact test was used, considering that the differences were statistically significant when $p < 0.05$.

RESULTS

A total of 428 SUS users accepted to participate of this study with a mean age of 41 years (DP: 13.69, minimum: 18, maximum, 79); 39,2% (n = 168) were HPV positive, with a mean age of 45 years (SD: 14.39; minimum: 27; maximum: 55), with 25.6% (n = 43) with less than 29 years old; 27.4% (n = 46) aged 30-39 years; 17.3% (n = 29) between 40-49 years. There were 8.3% and 2.4% of women between 60-69 years and 70-79 years. Of the total women in the study 60.8% (n = 260) were negative for HPV with mean age of 45 years (DP16.85, minimum: 18, maximum: 79).

Regarding ethnicity, the two groups had the majority of brown women with 61.9% of those with HPV positive and 65.4% with negative HPV. The majority of women who tested positive for HPV were married, 44.6% (n= 75). Regarding schooling, the majority attended elementary school, with 47% (n= 79) among those who were detected for HPV and 50% (n = 130) those who had negative results. As for income below two minimum wages, this condition was observed in 81% (n = 136) of women with positive HPV infection and 76.9% (n = 200) of women with HPV negative. Regarding the last colposcopy examination, the frequency of women who performed the test more than one year was greater in women detected with HPV 51.8% (n = 87) than those who were negative for the infection (46.2% n = 120). The demographic, sexual, and reproductive characteristics of the study sample are shown in Table 1.

Table 1. Sociodemographic characteristics of asymptomatic women in northeastern Brazil.

Category	HPV positive N (%)	HPV negative N (%)
Age Group		
Up to 29 years	43 (25.6)	52 (20)
30 to 39 years	46 (27.4)	79 (30.4)
40 to 49 years	29 (17.3)	56 (21.5)
50 to 59 years	32 (19)	47 (18.1)
60 to 69 years	14 (8.3)	18 (6.9)
70 to 79 years	4 (2.4)	6 (2.3)
Standard deviation		
Minimum	18	18
Maximum	79	79
Ethnicity		
White	49 (29.1)	72 (27.7)
Brown	104 (61.9)	170 (65.4)
Black	9 (5.4)	13 (5)
Yellow	6 (3.6)	4 (1.5)
Indigenous	0 (0.0)	1 (0.4)
Conjugal Situation		
Single	37 (22)	37 (14.2)
Married	75 (44.6)	151 (58.1)
Widow	15 (8.9)	17 (6.5)

Category	HPV positive N (%)	HPV negative N (%)
Separated	15 (8.9)	24 (9.2)
Consensus Union	26 (15.5)	31 (11.9)
Education		
None	10 (6)	12 (4.6)
DK / Refused	1 (0.6)	1 (0.4)
Elementary School	79 (47)	130 (50)
High school	65 (38.7)	78 (30)
Higher education	13 (7.7)	39 (15)
Income		
I do not have income	17 (10.1)	26 (10)
Less than 1 S.M	49 (29.2)	58 (22.3)
1 to less than 2 S.M	70 (41.7)	116 (44.6)
From 2 to less than 3 S.	20 (11.9)	35 (13.5)
From 3 to less than 5 S.M	10 (6)	14 (5.4)
5 to less than 10 S.M	2 (1.2)	5 (1.9)
DK / Refused	0 (0.0)	6 (2.3)
Carry out the last preventive exam		
1 year or less	64 (38.1)	103 (39.6)
More than 1 year	87 (51.8)	120 (46.2)
Never	12 (7.1)	18 (6.9)
Do not know	5 (3)	19 (7.3)
IST History		
Yes	11 (6.5)	13 (5)
No	157(93.5)	247(97)
Category	168 (100)	260 (100)

After relating the cofactors with the presence of HPV infection (Table 2), an association of HPV with the following variables was observed: use of oral contraceptives ($p < 0.016$) and alcohol use ($p < 0.038$). The prevalence of HPV was higher in the group that reported using oral contraceptives as a contraceptive method and in those who did not have any alcohol habits. The association between results for HPV and age showed a higher frequency of HPV positive in women older than 25 years (88.7%). There was a higher prevalence of the HPV virus in women who admitted to having had up to 5 sexual partners during the life (93.4%), until 3 pregnancies (71.4%) and with the cytopathological result within the limits of normality (61.9%), however, there was no statistical significance. Through the relationship between the human papillomavirus infection and the risk factors for cervical cancer, it was possible to verify that the majority of women were not smokers independent of the result for HPV infection.

Regarding cytopathologic reports (Table 3), HPV was identified in 40.3% (104/258) of the women with results within the limits of normality and 37, 6% (64/170) of women with some type of alteration identified. The types of alterations found were inflammation in 39.7% (158/428), atypical squamous cells of

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undetermined significance - ASC-US in 2.1% (9/428), atypical glandular cells - AGC in 0.5% (2/428), and atypical squamous cells not excluding intraepithelial lesion - ASC-H in 0.23% (1/428).

Table 2. Human papillomavirus infection and risk factors for cervical cancer in asymptomatic women in northeastern Brazil.

Variable	HPV+ N	HPV- N	OR (CI 95%)	P-value
Age				
Less than 25	19	21	1.45 (0.75 – 2.78)	0.308
More than 25	149	239		
First Sexual Relationship (years)				
Under 15	33	41	1.31 (0.79 – 2.17)	0.360
Greater than 15	135	219		
Number of Partners				
Up to 5	157	243	1.00 (0.46 – 2.19)	1.000
More than 5	11	17		
Use of Oral Contraceptives				
Yes	37	33	1.94 (1.15 – 3.26)	0.016
No	131	227		
Smoking				
Yes	23	25	1.49 (0.82 – 2.72)	0.211
No	145	235		
Ethicism				
Yes	59	66	1.59 (1.04 – 2.43)	0.038
No	109	194		
Cytopathological Result				
Normal	164	253	1.13 (0.33 – 3.94)	1.000
Changed	4	7		

Table 3. Cytopathological reports of asymptomatic women according to the type of alteration found

Type of Change	N (%)
Inflammation	158 (36.9)
ASC-US	9 (2.1)
AGC-US	2 (0.5)
ASC-H	1 (0.2)
Total	170 (39.7)

DISCUSSION

The detection of HPV infection in SUS users with more sensitive

and specific techniques to complement cytology may provide better screening¹⁰. In our study were identified by the PCR method, 39.2% (n = 168) positive, a higher frequency than in the Souza study (2016)¹¹, in which 16.3% of tested women were HPV positive by the PCR method. Although estimates vary by population, efforts have been made to know the incidence of this virus, considering that HPV is what most induce new cancers nowadays. Associated with knowledge of other cancer risk factors, it can enable close monitoring in order to improve diagnostic accuracy and more effective prevention.

The age distribution demonstrated that the most prevalent were women over the age of 25 years old, including those with cervical HPV infection, belonging to the risk group for cervical cancer incidence that is evidenced in young women between 20-29 years old and with higher risk between 45-49 years old¹². In this study, the HPV positivity showed that the age group over 25 years old is also more frequent, since in women under 30 years of age, most HPV infections regress spontaneously; however, in women over the age of 40, this infection may become persistent¹². A low socioeconomic and educational level was observed in both women with positive detection for HPV and those with negative results. Women with low socioeconomic status are at increased risk group for cervical HPV infection attributed to lack of screening, treatment of precancerous lesions, and knowledge of the prevalence of this infection¹³.

There was an expressive number of married women with HPV infection (44.6%). This fact may be due to exposure to infectious diseases due to sexual intercourse without using barrier methods¹⁴. The early onset of sexual life, the greater number of partners, multiparity, and smoking habits showed no significant relation with the positive detection of HPV. However, in other populations, behavioral factors such as multiple partners and early onset of sexual activity influence the risk of HPV infection^{15,16}, since they increase the likelihood of finding an infected partner. Multiparity is also associated with HPV infection due to pregnancy-induced hormonal changes facilitating direct exposure of the virus and other co-factors¹⁷. Smoking has been considered as one of the risk factors for cervical cancer because it interferes with the prevalence of HPV infection¹⁸.

Regarding the use of oral contraceptives, the frequency was higher in those who reported using it as a contraceptive method. Studies suggest that oral contraceptives may act as an important co-factor in the risk of cervical cancer in women with cervical HPV positivity¹⁹. Hormones present in oral contraceptives may alter the susceptibility of cervical cells to infection, affecting their ability to fight infection or facilitate HPV infection causing changes that progress to cervical cancer²⁰.

HPV detection in women with cytopathologic findings within the limits of normality was 40.3% (104/258). In our study, the prevalence of HPV was higher than that found by Vieira et al.²¹, with university students from the northern region of

Brazil, in which the prevalence of HPV in women with normal cytology was 23.4% (53/227). The overall prevalence of cervical HPV infection in normal cytologies in meta-analyse showed prevalence estimated between 8.4% and 29%²². The presence of HPV in women with cytology within the limits of normality suggests clinical latency and may evolve to spontaneous clearance, or depending on the risk factors in which it will be exposed, develop neoplastic lesions in the cervix²³.

Among the benign cellular alterations, inflammation was the most frequent finding of the cytopathological exams, corroborating with other studies. This inflammatory process impairs the quality of the sample, so it is necessary to perform the treatment to reduce the risk of lameness unsatisfactory²⁴. Inflammatory processes in the cervix act in the transformation zone, stimulating the development of squamous metaplasia, favoring cervical oncogenesis, since these cells are more permissive to HPV infection and its replication²⁵.

The result of atypical squamous cells of undetermined significance (ASC-US) is an expression of diagnostic uncertainty between normal and low-grade intraepithelial lesion²⁶ and ASC-H are atypical signs of undetermined significance in squamous cells, suggestive, but not diagnostic of intraepithelial lesion of high grade²⁷. Our study also identified atypical, mostly transient, but some may indicate a pre-malignant condition or more rarely invasive cancer²⁸. Cellular atypia of glandular cells was frequent in 0.5% of the population, which corroborates with studies, in which the incidence ranges from 0.1% to 0.8%³⁵. The finding of this atypia is important because the number of cases associated with pre-malignant lesions and cervical cancer is higher than for ASC-US²⁹.

Screening for HPV cervical infection is an important diagnostic finding, which is associated with the identification of other risk factors for a particular population, may provide more effective preventive measures and consequently stop the development of cervical cancer. More effective screening with more sensitive detection techniques, less susceptible to errors due to the subjectivity of the analysis, would be more effective tools to reduce the high incidence by potentiating early treatments,

reducing the development of new cases of cervical neoplasia.

CONCLUSION

In this study, we identified that 39.2% of the women had an HPV infection. Interestingly, a high frequency of infected women presented cytopathological examination results within the limits of normality, suggesting clinical latency. Thus, a prospective cohort study with this population would contribute to a better analysis of co-factors for the development of HPV infection. The variables that showed a relation to HPV positive and consequent risk factors for the development of cervical cancer were: alcoholism and the use of oral contraceptives.

This research favors the assistance to the woman directed to the prevention of these diseases, the sensitization of the population on the need for behavior change, and strengthening of knowledge about prevention and screening of cervical cancer. It should be noted that the insertion of HPV identification into the routine of the SUS would provide better screening of women who are at greater risk for the development of cervical cancer. The study reinforces the important role of HPV detection and risk factors related to susceptibility to cervical oncogenesis, suggesting that this type of cancer could be potentially preventable, since the risk factors are mostly controllable, and it is necessary to propose interventions that aim at the health education of this population, actions of prevention and early detection with the aid of molecular detection. Screening for the HPV virus is important to prevent the course of infection and subsequent development of cervical cancer and even in the pathology tracking system, the incidence is still high, so early detection enhances healing, avoiding the development of new cases of cervical neoplasia.

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