Human papillomavirus and risk factors for cervical adenocarcinoma in the state of Pernambuco, Brazil

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Abstract

Objectives: to determine the incidence of the main high oncogenic risk types of the human papillomavirus (HPV) (16, 18, 31 and 33) and the risk factors for cervical adenocarcinoma.

Methods: a case-control study was carried out with 324 women (69 with adenocarcinoma and 260 healthy controls) between 2001 and 2014. Information on risk factors associated with adenocarcinomawere collected and the detection performed on HPVby using Polymerase Chain Reaction (PCR) method.

Results: adenocarcinoma was associated with age ≥40 years old (OR=2.95; 95%CI=1.13-7.71), ≤3 years of schooling (OR=2.34; 95%CI=1.02-5.37), presence of HPV (OR=6.75; 95%CI=2.41-18.91),women in menopausal status (OR=4.76; 95%CI:1.70-13.31) black race (OR=6.71; 95%CI= 2.11-21.32) and never had undergone cervical cancer screening (OR=9.92; 95%CI:2.41-40.81). Andamong the HPV types detected, HPV 18 was observed to be strongly associated with adenocarcinoma of the cervix (OR=99.1; 95%CI=12.96-757.78).

Conclusions: the factors associated with cervical adenocarcinoma were ≥40 years old, ≤3 years of schooling, black race, menopausal status, never had undergone cervical cancer screening and the presence of HPV.

Key words *Adenocarcinoma in situ, Papillomaviridae, Molecular biology,Risk factors, uterine cervical neoplasms*

http://dx.doi.org/10.1590/1806-93042019000300009

Introduction

Cervical cancer is the fourth most common type of cancer worldwide, with 266,000 women's death occurred in 2012.[1] In Brazil, cervical cancer is the third most common type of cancer in women and the highest in mortality, excluding non-melanoma skin, with an estimated incidence of 17.1 cases per 100,000 women in 2018.[2]

Oncotic cytology is the well-established method used for screening precursor lesions and cervical cancer.[3] Even in developed countries with a good coverage, an increase has been observed in the incidence of cervical adenocarcinoma,[2] which is less common and more difficult to diagnose than squamous cell carcinoma, presenting more false negatives in screening, besides having a bad prognosis andunsatisfiedtherapeutic response.[4]

There has been an increase in the incidence of cervical glandular neoplasia over the past thirty years, with these now accounting for 24% of all cancer cases diagnosed in the United States annually.[5] Of all invasive carcinomas of the uterine cervix, 27% are adenocarcinomas in their pre-invasive and invasive forms.[6]

Cervical adenocarcinoma is observed as an associated factor fornulliparity, excess weight, exogenous estrogen,6 better socioeconomic level, age <35 years[7] and human papillomavirus (HPV) type 16 and 18.[8]

The causal agent associated with squamous cell carcinoma and adenocarcinoma of the uterine cervix is HPV. In addition to factors related to the infection itself such as viral load and whether it consists of a single or multiple infections are associated to other HPV factors that can influence the progression or the disappearance of the disease.[9]

Therefore, this present study was carried out to determine the associated factors to cervical adenocarcinoma and besides the frequency of HPV typesin a poor region of Latin America, thus contributing withuseful information for an appropriate prevention and conduct for the patients.

Methods

An analytical, observational, case-control study was conducted. The study was based on the women's data assisted at the *Serviço de Patologia Cervical do CAM-IMIP*, (Cervix Pathology Service) at the *Instituto de Medicina Integral Prof. Fernando Figueira* (IMIP) between 2001 and 2014.

Sample size was calculated by using OpenEpi, version 2.3.1 (Atlanta, GA, USA), considering a smoking frequency of 50% in women with adenocarcinoma and 30% in the healthy controls.[10] For a case/control proportion of 1:4, a power of 80% and a 5% significance level, 64 cases and 256 controls would be required. To compensate for possible losses, the sample was increased by 20%, 77 cases and 308 controls.

Cases included all women with histopathological diagnosis of adenocarcinoma *in situ* or invasive cervical, as identified at the cervix pathology record service,any patient with adenocarcinoma for paraffin blocks from biopsy or surgical specimens were excluded. The healthy controls consisted of women submitted to routine cervical cancer screening whose data were used in the control case study conducted by Mendonça *et al.*[10]. Women whose cytology findings included a diagnosis of atypical cells or who had abnormal findings at colposcopy including suggestion of invasion were excluded from the controls.

For this study, altered cytology was taken in considerationwhen the results were abnormal according to the *Sociedade Brasileira de Citologia* (Brazilian Cytology Society).[3] Colposcopy was described as abnormal according to the definition established by the *Sociedade Brasileira de Patologia do Trato Genital Inferior e Colposcopia* (Brazilian Society of Pathology of the Lower Genital Tract and Colposcopy) and the International Federation for Cervical Pathology and Colposcopy (IFCPC).[11]

Eligible participants were identified from the records in the Cytology Department and divided into two groups. The independent variables were collected from the medical records before their diagnosis on adenocarcinoma. Paraffin blocks for biopsy or surgical specimen were used for genotyping.

The variables evaluated were *in situ* and invasive adenocarcinoma, age (years), skin color/race, body mass index (Kg/m^2), illiteracy, schooling,, absence of the partner, place of residence, age at first sexual intercourse and number of partners. Other variables included the number of previous pregnancies, menopausal status, prior use of hormonal contraceptives, condom use, use of immunosuppressive drugs, chronic diseases, sexually transmitted infections, and smoking, underwent cancer screening and frequency of HPV types.

HPV genotype was obtained for the controls following the *cytobrush* sampling, with HPV-DNA testing was performed in six genotypes (HPV 16, 18, 31, 33, 6 and 11) using specific primer.[10] The material for viral genotyping was stored in 10mM Tris-HCl, and the DNA of the HPVwas extracted by using Genomic® DNA Purification kit (Promega

Corporation, Madison, WI, USA). The quality of the DNA target sequence was tested in each sample by using the MY09/MY11.[10]

In the case group, the DNA of the HPV was extracted from three 10-µm paraffin-embedded tissue sections from the biopsy specimens using the QiAamp DNA FFPE Tissue Kit (Qiagen GmbH, Hilden, Germany). The quality of the DNA target sequence and the absence of the inhibitors were tested in each sample by using the MY09/11 and GP5+/6+ primers for the amplification of the DNA viral and the PC04/GH20 primers for the internal control group. (human β-globin gene). Specific primers were used for HPV types 16, 18, 31 and 33.[10]

The data were collected using a specifically form developed by the own researcher. Data analysis was conducted by using Epi Info, version 7.1 (Atlanta, GA, USA). Initially, distribution tables were obtainedof the frequencies of the categorical variables and by the frequency determined by the HPV genotypes.

To determine the association between the dependent variable, cervical adenocarcinoma, and the independent variables or predictors, the chi-square test and Fisher's exact test were used when it was appropriate.

The *odds ratios* (OR) and 95% confidence intervals (95%CI) were calculated to determine the strength of the association between the dependent and independent variables as an estimate of relative risk. In all the steps of the analysis, a significance level of 5% was adopted and all *p*-values were two-tailed. Next, a multivariate, hierarchical stepwise logistic regression analysis was performed.[12] A table was then constitutedwith the final variables that remained associated with adenocarcinoma.

This study was approved by the Ethics Research in Human Beings Committee at IMIP under the protocol number: CAAE 10815112.9.0000.5201. All the women were invited to participate in the study and only the women who voluntarily agreed to participate and signed an informed consent form were included.

Results

Seventy-seven women with a histopathological diagnosis of cervical adenocarcinoma were selected at the pathology departmentat IMIP. Of those, 13 patients whose blocks were absent, were excluded from the study. The study consisted of 64 cases, one of these women (1.6%) had adenocarcinoma *in situ* and 63 (98.4%) had invasive adenocarcinomas. The stage distribution (I, II, III, and IV) of women with invasive adenocarcinoma was 19 (30.1%), 17 (27.1%), 19 (30.1%) and 8 (12.7%)respectively. For the control group, 304 women were selected from a study conducted by Mendonça *et al.*[10], however 44 were excluded because of some abnormality in their cytology and/or colposcopy results, now having 260 controls.

In Table 1, a bivariate analysis was carried out in relation to biological and socio-demographic factors and it was observed that women who presented adenocarcinoma had a higher frequency in women aged higher or equal to 40 (OR=3.74; CI95%=1.94-7.22; $p<0.0001$), who were black (OR=3.19; CI95%= 1.32-7.74; $p=0.02$) and ≤3 years of schooling (OR=5.37; CI95%=2.84-10.16; $p<0.0001$) when comparing to healthy women. It was also observed that women who had adenocarcinoma, living in Recife and in the surrounding metropolitan area were found to constitute a protective factor (67.2% *versus* 83.8%; OR=0.39; CI95%=0.21-0.73; $p=0.002$).

The reproductive factors, lifestyle-related and immunological variables were significantly associated with cervical adenocarcinoma (Table 1) including the number of partners, ≤2 partners (71.2% *vs* 56.5%; OR=1.92; CI95%=1.02-3.61; $p=0.04$); >5 previous pregnancies (30% *vs* 10.8%; OR=3.55; CI95%=1.80-6.99; $p=0.0001$); previously used oral contraception (39.7% *vs* 73%; OR=0.24; CI95%= 0.13-0.44; $p<0.0001$). Other associated factors included menopausal status (29.8% *vs* 7.3%; OR=5.39; CI95%=2.58-11.24; $p=0.0001$), the presence of chronic diseases (65.1% *vs* 36.7%; OR=3.22; CI95%=1.81-5.72; $p<0.0001$) and women who had not undergone cervical cancer screening (29.3% *vs* 2.3%; OR=17.5; CI95%=6.54-47.12; $p<0.0001$) (Table 1).

Table 2 shows the factors that remained associated with cervical adenocarcinoma in the multivariate analysis, which included ≥40 years old (OR=2.95; CI95%=1.13-7.71; $p=0.03$); schooling ≤3 years (OR=2.34; CI95%=1.02-5.37; $p=0.04$) and the presence of HPV (OR=6.75; CI95%=2.41-18.91; $p=0.0003$). In addition, menopausal status (OR=4.76; CI95%=1.70-13.31; $p=0.003$), black (OR=6.71; CI95%=2.11-21.32; $p=0.001$) and have never undergone previous cervical cancer screening (OR=9.92; CI95%=2.41-40.81; $p=0.001$) also remained significantly associated with adenocarcinoma.

To study the associations of HPV types 16, 18, 31 and 33 with cervical adenocarcinoma, two different manners were evaluated: no other type of

Table 1

Factors associated with cervical adenocarcinoma.

Variable	Adenocarcinoma				OR	CI95%	*p*
	yes		no				
	n	%	n	%			
First sexual intercourse							0.62*
< 20 years old	40	71.4	177	68.1	1.17	0.62-2.21	
> 20 years old	16	28.6	83	31.9			
Number of partners							0.04*
< 2	40	71.2	147	56.5	1.92	1.02-3.61	
> 2	16	28.6	113	43.5			
Previous pregnancies							<0.001*
>5	18	30.0	28	10.8	3.55	1.80-6.99	
<5	42	70.0	232	89.2			
Previous use of hormonal contraceptives							<0.001*
Yes	23	39.7	189	73.0	0.24	0.13-0.44	
No	35	60.3	70	27.0			
Menopause							<0.001*
Yes	17	29.8	19	7.3	5.39	2.58-11.24	
No	40	70.2	241	92.7			
Condom use							0.16**
Yes	1	1.8	20	7.7	0.21	0.03-1.63	
No	56	98.2	240	92.3			
Immunosuppressive drugs							0.7**
Yes	0	0	5	1.9	-	-	
No	60	100	255	98.1			
Chronic disease							<0.001*
Yes	41	65.1	95	36.7	3.22	1.81-5.72	
No	22	34.9	164	63.3			
STI							0.11*
Yes	6	9.8	47	18.4	0.48	0.19-1.19	
No	55	90.2	209	81.6			
Current smoker							0.27*
Yes	3	5.1	25	9.6	0.50	0.15-1.73	
No	56	94.9	235	90.4			
Former smoker							0.97*
Yes	13	22.0	52	22.2	0.99	0.49-1.97	
No	46	78.0	182	77.8			
Smokes							0.24*
Yes	13	22.0	77	29.7	0.67	0.34-1.31	
No	46	78.0	182	70.3			
Cancer screening							<0.001**
No	17	29.3	6	2.3	17.5	6.54-47.12	
Yes	41	70.7	254	97.7			
HPV							<0.001*
Yes	56	87.5	146	56.2	5.47	2.50-11.93	
No	8	12.5	114	43.8			
Age ≥40 years old							<0.001*
Yes	51	79.7	133	51.2	3.74	1.94-7.22	
No	13	20.3	127	48.8			

continue

*Chi-square test, **Fisher's exact test, STI= sexually transmitted infection, OR: *Odds Ratio*, CI95%= 95% confidence interval, HPV= human papillomavirus, BMI= body mass index.

Table 1 **concluded**

Factors associated with cervical adenocarcinoma.

Variable	Adenocarcinoma				OR	CI95%	*p*
	yes		no				
	n	%	n	%			
Blackskin							
Yes	9	16.4	15	5.8	3.19	1.32-7.74	0.02**
No	46	83.6	245	94.2			
BMI ≥25.0 kg/m²							
Yes	25	64.1	138	56.8	1.34	0.67-2.74	0.39*
No	14	35.9	105	43.2			
Illiterate							
Yes	9	17.6	11	4.2	4.85	1.89-12.41	0.004**
No	42	82.4	249	95.8			
Schooling ≤3 years							
Yes	27	52.9	45	17.3	5.37	2.84-10.16	<0.001*
No	24	47.1	215	82.7			
No current partner							
Yes	26	44.1	77	29.6	1.87	1.05-3.34	0.03*
No	33	55.9	183	70.4			
Lives in Recife or in the metropolitan region							
Yes	43	67.2	218	83.8	0.39	0.21-0.73	0.002*
No	21	32.8	42	16.2			

*Chi-square test, **Fisher's exact test, STI= sexually transmitted infection, OR= *Odds Ratio*, CI95%= 95% confidence interval, HPV= human papillomavirus, BMI= body mass index.

Table 2

Multivariate analysis of factors associated with cervical adenocarcinoma.

Variables	Adenocarcinoma				
	Coefficient	Standard Error	OR	CI95%	*p*
Age ≥40 years old	1.08	0.49	2.95	1.13-7.71	0.03
Schooling ≤3 years	0.85	0.42	2.34	1.02-5.37	0.04
HPV	1.91	0.52	6.75	2.41-18.91	<0.001
Menopause	1.56	0.52	4.76	1.70-13.31	0.003
Blackskin	1.90	0.59	6.71	2.11-21.32	0.001
Never underwent screening	2.29	0.72	9.92	2.41-40.81	0.001
Constant	-4.80	0.62	-	-	<0.001

*Chi-square test, OR= *Odds Ratio*, CI95%= 95% confidence interval, HPV= humanpapillomavirus.

Table 3

HPV types associated with women with cervical adenocarcinoma.

HPV	Women with adenocarcinoma		Healthy women		OR	CI95%	*p*
	n=64	%	n=219	%			
16	34	53.1	90	41.1	1.62	0.93-2.84	0.09*
18	20	31.3	1	0.5	99.1	12.96-757.78	<0.001**
31	33	51.6	40	18.3	4.76	2.62-8.66	<0.001*
33	27	42.2	7	3.2	22.10	8.97-54.45	<0.001*
16 alone	13	20.3	58	26.5	0.71	0.36-1.39	0.32*
31 alone	7	10.9	14	6.4	1.80	0.69-4.67	0.17**
33 alone	4	6.3	0	0	-	-	0.004**
16, 18 together	3	4.7	0	0	-	-	0.01**
16, 18 associated with other types	14	21.9	0	0	-	-	<0.001**
16, 31 together	1	1.6	25	11.4	0.12	0.02-0.93	0.04**
16, 31 associated with other types	16	25.0	25	11.4	2.59	1.28-5.22	0.007*
16, 33 together	0	0	7	3.2	-	-	0.32**
16, 33 associated with other types	14	21.9	7	3.2	8.48	3.25-22.11	<0.001**
18, 31 together	2	3.1	1	0.5	7.03	0.63-78.85	0.13**
18, 31 associated with other types	14	21.9	1	0.5	61.04	7.84-475.07	<0.001**
18,33 together	1	1.6	0	0	-	-	0.46**
18, 33 associated with other types	12	18.8	0	0	-	-	<0.001**
31, 33 together	5	7.8	0	0	-	-	0.001**
31, 33 associated with other types	20	31.3	0	0	-	-	<0.001**
16, 18, 31 together	9	14.1	0	0	-	-	<0.001**
16, 18, 33 together	8	12.5	0	0	-	-	<0.001**
16, 31, 33 together	12	18.8	0	0	-	-	<0.001**
18, 31, 33 together	9	14.1	0	0	-	-	<0.001**
16, 18, 31, 33 together	6	9.4	0	0	-	-	<0.001**

*Chi-square test, **Fisher's exact test, OR= *Odds Ratio*, CI95%= 95% confidence interval, HPV= human papillomavirus.

HPV alone or in association to one or more types of HPVwere detected in the same patient Thus, we observed that HPV 18 presented a strong association with cervical adenocarcinoma (OR=99.1; CI95%=12.96-757.78) but only when associated with one or more types of HPV. It should be emphasized that HPV 18 alone was not observed in our sample. Conversely, the presence of HPV 16 alone (OR=0.71; CI95%=0.36-1.39; *p*=0.32) or together with one or more HPV types (OR=1.62; CI95%=0.93-2.84; *p*=0.09) did not show any association with adenocarcinoma. As for HPV 33, a significant association was found while alone (*p*=0.004) and in association with one or more other HPV types (OR=22.1; 95%CI=8.97-54.45) (Table 3).

Discussion

In this present study, we have observed that women aged ≥40 years old, who had ≤3 years of schooling, had the presence of HPV, particularly HPV 18 associated with other HPV types, menopause, blackskin and never have undergone cervical cancer screening were factors strongly associated with adenocarcinoma.

Studies report that the time of appearance of cervical adenocarcinoma has been decreasing over recent years.[1,5-7] In this present study, women aged ≥40 years old and presented menopause were factors associated with adenocarcinoma, unlike in other studies in which this association was found in younger ages.[13] This difference,along with the worldwide trends, may be due to delays in the diagnosis of adenocarcinoma in Brazil where in fact, the access to healthcare services is often difficult and this may have contributed to this association.[10]

Furthermore, as most of the patients in this study were diagnosed in the invasive phase, the age group involved may have been younger if earlier stages of the disease had been predominant. Epidemiological studies conducted between 1986 and 2005 revealed an increase in the incidence of cervical adenocarcinoma in women up to 35 years of age,[13] particularly between 20 and 34 years old.[13] While in 2007, a study conducted in Porto Alegre, Brazil, found that the patients' mean age with adenocarcinoma was 53.2 years old,[14] a figure similar to that in this study.

The association among schooling ≤3 years, blackskin and never have undergone cervical cancer screening is closely associated with low socioeconomic conditions of this population. This finding differs from other authors in which report an increase in the incidence of cervical adenocarcinoma in populations with a higher socioeconomic level.[8,15] It is important to emphasize that most of the studies on adenocarcinoma were conducted in developed countries,[16] however, this study was carried out in a poor region of a developing country, in the Northeast of Brazil. Low socioeconomic level is associated with problems in seeking and having access to healthcare services; consequently, cervical cancer screening tests are not performed.

The lack of cervical cancer screening was an important factor for the presence of neoplasms, with an approximately 10-fold chance for women with cervical adenocarcinoma to have not undergone any kind of screening. This result shows the need for more effective screening program with better coverage similar to the developed countries.[1] The lack of access to the healthcare services may have contributed in not performing the screening, thus, women with adenocarcinoma were, less likely, living in Recife or in the metropolitan area in the state of Pernambuco, where the coverage is better than in other areas of the state.

Obesity and the use of contraceptives are described as factors associatedwith adenocarcinoma, however, this association was not found. The lack of association may be due to a general profile of overweight people in this state.[17] Moreover, this study evaluated overweightbut not obesity. In relation to the duration of contraceptive use, it was not analyzed, and most studies have related thedurationof use with the presence of the disease, although theseresults are controversial.[16,18]

No significant associations were found for cervical adenocarcinoma in sexually transmitted infections or the use of immunosuppressive,possibly this information was missing on some records, for this is already known as a risk associated factor.[19] Similarly, the use of condoms protect patients against adenocarcinoma;[20] however, in our present study this association was not observed. As the data collection was retrospective, the information was not always available. In relation to smoking, there was no significant association in which corroborates with most of the studies.[15,21]

The presence of HPV was 87.5% in the case groups. The literature refers to the presence of HPV 16 and 18 in up to 90% of the cases of adenocarcinoma in situ[19] and in 92% of the cases of invasive adenocarcinoma.[20] Among the types of HPV mostly found, HPV 18 was closely related with adenocarcinoma; however, it was always associated tosome other type or more than one different HPV types. There were no findings of HPV 18 alone in either case or control groups. HPV 33 with no association

to other HPV types, but some types of associations werefound only in the case group, and there are no other similar results observed in the researched literature.

Studies suggest that association between different HPV types is important for the occurrence of adenocarcinoma.[21,22] The present findings showed that the likelihood of adenocarcinoma was greater when HPV 18 and 31 were associated with other types. The literatureshowed that HPV 16 and 18 together are responsible for 70% of the cervical cancer cases worldwide.[23]

In a Brazilian study, the most common HPV types found in women with adenocarcinoma were HPV 16 (77.6%), 18 (12.3%), 31 (8.8%), 33 (7.1%) and 35 (5.9%), like the findings in this present study.[22] However, in that study only 28 cases consisted of adenocarcinoma. Other data in the literature have reported the most common types of HPV in adenocarcinoma are HPV 16 (41.6%), 18 (38.7%), 45 (7.0%), 31 (2.2%) and 33 (2.1%), in which did not occur in the present study.[23]

There are some methodological limitations to this study. As this study is retrospective, there were some difficulties in the research of someinformation missing. And additionally, 13 cases were excluded because tissue paraffin blocks for genotyping were not found. Another limitation concerns the consequence of using different HPV typing methods for the cases and controls. Nevertheless, it should be emphasized that amplification of the human beta-globin gene was performed in both groups, guaranteeing the presence of DNA in the sample despite the difficulties described in the literature. All the paraffin-embedded samples case groupswere tested positive for the human beta-globin gene.[24]

In conclusion, further studies are required to correlate HPV types in women with cervical adenocarcinoma and to evaluate their variation in each region precisely at the time of diagnosis, making this investigation part ofhospitals routine. These studies should contribute to provide further knowledge on the behavior of HPV in cases of cervical adenocarcinoma. Likewise, it is important to continue analyzing the associated factors in new epidemiological studies. Since the frequency of adenocarcinoma is low, the optimal study design is a case-control study such as this one, because the design study are more factual to determine these factors.

We believe that this scenario could change if vaccination coverage against HPV types 6, 11, 16 and 18 were 100%, since HPV 18 is closely associated with adenocarcinoma.However, it is generally accompanied by other types such as HPV 16, 31 and 33, as found in this study. In the future changes may occur both in the viral types and in the variants of these types and even vaccination campaigns may require more regionalized re-organization.

Contribuições dos autores

Souza ASR and Amorim MMR - performed all the data handling and statistical analyses. Souza PRE contributed to the methodological discussions. Costa TML and Souza ASR - drafted the first version of the article. Souza ASR, Amorim MMR, Costa TML, Souza PRE, Heráclio S, Souza GFA and Lubambo N revised the article on several occasions. All authors approved the final version of the manuscript.

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Received on January 15, 2019

Final version presented on April 15, 2019

Approved on June 19, 2019