Journal of Nursing
UFPE On Line
ISSN: 1981-8963

J Nurs UFPE on line.
2020;14:e244212
DOI: 10.5205/1981-8963.2020.244212
https://periodicos.ufpe.br/revistas/revistaenfermagem

ORIGINAL ARTICLE

PERSISTENCE OF HPV IN WOMEN TREATED FOR CERVICAL ADENOCARCINOMA

PERSISTÊNCIA DO HPV EM MULHERES TRATADAS PARA O ADENOCARCINOMA CERVICAL

PERSISTENCIA DEL VPH EN MUJERES TRATADAS POR ADENOCARCINOMA CERVICAL

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ABSTRACT

Objective: to determine the frequency of persistence of HPV in women treated for cervical adenocarcinoma. ***Method:*** this is a quantitative, descriptive, retrospective, cohort study, with 77 women genotyped for HPV before treatment and with cervical adenocarcinoma. New cervical secretion material was collected after treatment to detect HPV DNA by polymerase chain reaction. The Epi Info 7.1.4 statistical program was used for data analysis. ***Results:*** it was observed that, out of 77 patients, it was possible to determine HPV genotyping after treatment in 30 women, and of these, seven (23.3%) had detectable HPV. HPV types were found, of which four patients (57.1%) had HPV 31, and in one patient it was associated with HPV 18; o 33 in two women (28.6%), one of whom was associated with HPV 16 and one had HPV 11 and 56 associated (14.2%). ***Conclusion:*** HPV was detected in cervical secretion in 23.3% of women after treatment for cervical adenocarcinoma, with HPV 31 being the most frequent type. ***Descriptors:*** Adenocarcinoma; Papillomaviridae; Treatment Failure; Prevalence; Cervix Uteri; Sexually Transmitted Diseases.

RESUMO

Objetivo: determinar a frequência da persistência do HPV em mulheres tratadas para o adenocarcinoma cervical. ***Método:*** trata-se de um estudo quantitativo, descritivo, retrospectivo, do tipo coorte, com 77 mulheres genotipadas para o HPV antes do tratamento e com adenocarcinoma cervical. Coletou-se novo material de secreção cervical após o tratamento para a realização da detecção do DNA do HPV por reação de cadeia da polimerase. Utilizou-se o programa estatístico Epi Info 7.1.4. para a análise dos dados. ***Resultados:*** observou-se que, das 77 pacientes, foi possível determinar a genotipagem do HPV após o tratamento em 30 mulheres e, destas, 7 (23,3%) apresentaram o HPV detectável. Encontraram-se os tipos de HPV dos quais quatro pacientes (57,1%) estavam com o HPV 31, sendo que, em uma paciente, estava associado ao HPV 18; o 33 em duas mulheres (28,6%), sendo que em uma estava associado ao HPV 16 e uma apresentou os HPV 11 e 56 associados (14,2%). ***Conclusão:*** detectou-se o HPV na secreção cervical em 23,3% das mulheres após o tratamento para o adenocarcinoma de colo uterino, sendo o HPV 31 o tipo mais frequente. ***Descritores:*** Adenocarcinoma; HPV; Falha de Tratamento; Prevalência; Colo do Útero; Doenças Sexualmente Transmissíveis.

RESUMEN

Objetivo: determinar la frecuencia de persistencia del VPH en mujeres tratadas por adenocarcinoma cervical. ***Método:*** estudio de cohorte cuantitativo, descriptivo, retrospectivo, con 77 mujeres genotipadas para el VPH antes del tratamiento y con adenocarcinoma cervical. Se recogió nuevo material de secreción cervical después del tratamiento para detectar el ADN del VPH por reacción en cadena de la polimerasa. Se utilizó el programa estadístico Epi Info 7.1.4. para el análisis de datos. ***Resultados:*** se observó que, de las 77 pacientes, fue posible determinar el genotipo del VPH después del tratamiento en 30 mujeres, y de estos, 7 (23.3%) tenían VPH detectable. Se encontraron tipos de VPH, de los cuales cuatro pacientes (57.1%) tenían VPH 31, y en una paciente se asoció con VPH 18; o 33 en dos mujeres (28,6%), una de las cuales estaba asociada con el VPH 16 y una tenía VPH 11 y 56 (14,2%). ***Conclusión:*** el VPH se detectó en la secreción cervical en el 23,3% de las mujeres después del tratamiento para el adenocarcinoma de cuello uterino, siendo el VPH 31 el tipo más frecuente. ***Descriptores:*** Adenocarcinoma; Papillomaviridae; Insuficiencia del Tratamiento; Prevalencia; Cuello del Útero; Enfermedades de Transmisión Sexual.

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How to cite this article
Costa TML, Morais AP, Gonçalves AL, Valadares MMS, Lubambo N, Souza GFA. Persistence of HPV in women treated for cervical adenocarcinoma. J Nurs UFPE on line. 2020;14:e244212 DOI: https://doi.org/10.5205/1981-8963.2020.244212

INTRODUCTION

Cervical adenocarcinoma is defined as a cancer of the cervix that occurs in the columnar epithelium, with an estimated incidence of 569,000 cases annually.[1] It is characterized by the replacement of the normal glandular epithelium, which presents an increase in the size of cells and their nuclei, nuclear hyperchromasia, mitotic activity and cell stratification. It can also be configured in situ, when limited to the superficial layer of the neck, or invasive, when it exceeds it.[2-3] In one study, approximately 59% of women with cervical cancer presented,[4] observing an increasing frequency in the last years.[5]

It is understood that cervical cancer is a neoplasm with the possibility of prevention and great chances of cure, when discovered and treated early. It is known to be the fourth leading cause of cancer death[6] and the second most frequent in women from all over the world.[7] In Brazil, it is evidenced as being the second cause of cancer morbidity and mortality among women, being surpassed only by breast cancer[6]. It is also expected that there will be a 22% increase in the absolute death rate by 2030.[8]

Human Papilloma Virus (HPV) is associated with cervical cancer in 99% of patients.[7] In addition, there is a higher prevalence of cervical cancer in low- and middle-income countries, with approximately 85% of cases and 87% of deaths worldwide, due to ineffective preventive measures against HPV associated with the lifestyle of these people (smoking, number of partners, diet and genetic condition).[1]

It is known that the treatment of cervical cancer occurs according to the clinical stage and the conditions of the patients, by surgery and/or chemotherapy and/or radiotherapy.[9] It is also noted that the prognosis depends on the clinical status, tumor size, histological type and involvement of the parametrium and lymph nodes, with adenocarcinoma having the worst prognosis in relation to cervical carcinoma.[10]

It is noteworthy that no treatment actually eradicates HPV, even with the treatment used for cervical cancer, which aims to remove the lesion to promote clinical improvement and prevent transmissibility. It is noteworthy; therefore, that even after some years of treatment, the lesion may recur or relapse, depending on the type of HPV, type of cancer and immunity of the patient.[11-2]

It appears that, among the data sources consulted, no studies were found relating the prevalence of HPV infection after treatment for adenocarcinoma. Only one study was found reporting its prevalence at the time of cervical cancer diagnosis,[13] without comparatives, too, as to its post-treatment outcome.

It is observed that the increase in the incidence of cervical adenocarcinoma has been unaccompanied by knowledge about the prevalence of HPV in women undergoing treatment, making new researches of great importance.

OBJECTIVE

- To determine the frequency of HPV persistence in women treated for cervical adenocarcinoma.

METHOD

This is a quantitative, descriptive, retrospective, cohort study, which included all women undergoing treatment for cervical adenocarcinoma. Women who did not return or died at the time of contact were excluded. Adenocarcinoma was diagnosed by means of histopathological examination between 2001 and 2014, with data collection performed between 2015 and 2016.

Data collection was performed through the medical records of the patients identified in the colposcopy clinic. All patients who were candidates for entry into the study were contacted by phone or when they returned for the follow-up consultation and / or the researcher went to the patient's address, being invited to participate in the research.

The variables were studied: age; County; mesoregion; urban or rural area; state; breed; marital situation; occupation; schooling; age of first sexual intercourse; number of sexual partners; parity; contraceptive use; Pap smear examination prior to diagnosis; alcoholism; use of drugs; smoking; history of sexually transmitted diseases; Body Mass Index (BMI); genotyping of HPV in cervical secretion; genotyping of HPV in paraffin; staging; type of treatment used; evolution up to one year after treatment; evolution after five years of treatment; evolution after ten years of treatment and deaths.

Cervical secretion material was collected for viral detection after treatment of cervical cancer using a cytobrush. HPV DNA research was carried out for HPV genotyping 16, 18, 31 and 33 at the Federal Rural University of Pernambuco, in the Genome laboratory, Department of Biology, through the Polymerase Chain Reaction (PCR) in which primers MY 09/11 and GP5 + / 6 + were used to amplify viral DNA and primers RS42 and KM29 for internal control of the reaction.

The Epi Info 7.1.4 statistical program (Atlanta, GA, USA) was used for data analysis. Initially, frequency distribution tables were obtained for categorical variables and for determining the frequencies of HPV genotypes, in addition to calculating measures of central tendency and dispersion for numerical variables.

Approval was obtained by the Human Research Ethics Committee of the Professor Fernando Figueira Institute of Integral Medicine (IMIP) (Opinion no. 4,510-15 of 23 December 2014). Cervical secretion material was collected from patients who returned to the colposcopy clinic, after they agreed to participate and signed the Free and Informed Consent Form (FICT).

RESULTS

The study included 77 women treated for cervical adenocarcinoma (Table 1).

Table 1. Biopsychosocial characteristics in women with cervical adenocarcinoma. Recife (PE), Brazil, 2016.

Characteristics		
Origin (n=77)	**n**	**%**
MRR	49	63.6
Agreste	11	14.3
Zona da Mata	10	13.0
Sertão	7	9.1
Race (n=69)	**n**	**%**
Brown	36	52.2
White	19	27.5
Black	14	20.3
Education (n=65)	**n**	**%**
None	12	18.5
1-3 years	23	35.4
4-7 years	11	16.9
8-11 years	11	16.9
>12 years	8	12.3
Occupation (n=69)	**n**	**%**
Without Monetary Income	39	79.7
With Monetary Income	30	20.3
BMI Kg/M² (n=50): (Average ± SD)	27,9±13,6	
Overweight	35	70.0
Underweight	1	2.0
Illicit drugs (n=72)	**n**	**%**
	1	**1.4**
Drinking (n=70)	**n**	**%**
	8	**11.1**
Smoking (n=72)	**n**	**%**
	6	**8.3**
Use of hormonal contraceptives (n=61)	**n**	**%**
	28	**39.4**
Pap smear prior to diagnosis (n=70)	**n**	**%**
	52	**74.3**
Previous colposcopy with signs of invasion (n=63)	**n**	**%**
	44	**69.8**
Age at diagnosis in years (Average ± SD)	52,4 ± 13, 6	
Age 1st sexual intercourse in years (Average ± SD)	18,2 ± 3,8	
No. Partners (Median; IQR)	1; 1-3	
Parity (Median; IQR)	3; 2-6	

MRR: Metropolitan Region of Recife; BMI: Body Mass Index; SD: Standard deviation; IIR: Interquartile range. Source: IMIP (2001-2014).

In terms of clinical staging at the time of diagnosis, two are considered to be in stage 0 (2.6%); 23 (29.9%), in stage I; 21 (27.2%), in stage II; 22 (28.6%), in stage III and nine (11.7%), in stage IV (Table 2).

As for treatment, it was found that 26 (33.8%) patients underwent Associated Radiotherapy (RT) and Chemotherapy (CT), followed by Isolated Surgery (30.0%), Surgery, RT and Associated CT (10.4 %), Surgery and Associated RT (9.0%), Isolated RT (9.0%), Surgery and Associated CT (1.3%) and no treatment (6.5%). It is noteworthy that, in patients who underwent RT, brachytherapy may or may not be accompanied.

HPV 16 without associations was found to be the main type found in paraffin genotyping before treatment. It was identified, in the secretion after treatment, that seven (23.3%) had HPV, with type 31 being the most frequent, which was diagnosed in four patients (57.1%); of these, in three women, it was isolated (42.8%) and in one (14.3%), associated with type 18, which also demonstrated the same types in paraffin genotyping at the time of diagnosis. HPV 33 was diagnosed in two women, one in isolation (14.3%) and the other in association with HPV 16 (14.3%). It is noteworthy that HPV 11 and 56 associates were found in one patient (Tables 2 and 3).

Table 2. HPV genotyping before treatment in women with cervical adenocarcinoma. Recife (PE), Brazil, 2016.

Genotyping	n	%
Paraffin before treatment (n=64)		
16 without association	13	20.3
31 without association	7	11
33 without association	4	6.3
16, 18 associated	3	4.7
16, 31 associated	1	1.5
18, 31 associated	2	3.2
18, 33 associated	1	1.5
31, 33 associated	5	7.8
16, 18, 31 associated	3	1.7
16, 31, 33, associated	6	9.3
16, 18, 33 associated	2	3.2
18, 31, 33 associated	3	4.7
16, 18, 31, 33 associated	6	9.3

HPV: Human Papilloma Virus. Source: IMIP (2001-2014).

Table 3. HPV diagnosed before and after treatment of cervical adenocarcinoma and the treatment performed. Recife (PE), Brazil, 2016.

HPV after treatment	HPV before treatment	Treatment performed
1. 18, 31	18, 31	Surgery
2. 16, 33*	-	Surgery
3. 31*	-	CT + RT
4. 31*	-	Surgery
5. 31*	-	Surgery
6. 33*	-	Surgery
7. 11, 56	16, 18	CT + RT

*Patients 2 - 6 did not have a defined type of HPV before treatment by paraffin genotyping. CT: Chemotherapy; RT: Radiotherapy. Source: IMIP (2001-2014).

It is admitted that, in relation to the year of diagnosis of the patients, one (1.3%) was diagnosed in 2001; two (2.7%), in 2002; one (1.3%), in 2003; one (1.3%), in 2004; two (2.7%), in 2006; two (2.7%), in 2007; five (6.7%), in 2008; ten (13.3%), in 2009; nine (12%), in 2010; 13 (17.3%), in 2011; 16 (21.3%), in 2012; nine (12%) in 2013 and two (2.7%) in 2014.

It was configured that, in the evolution up to one year of treatment (Table 4).

Table 4. Evolution after treatment performed in women with cervical adenocarcinoma. Recife (PE), Brazil, 2016.

Evolution after treatment	n	%
1 year (N=73):		
Death	2	2.74
Persistence of the disease in colposcopy	3	4.11
Need for new surgery	2	2.74
Metastasis*	4	5.48
Other cancer**	2	2.74
Atypia	1	1.37
Without changes	46	63
5 years (N=75):		
Alteration in colposcopy	1	1.3
Metastasis***	2	2.6
Actinic retinitis	1	1.3
Death	11	14.7
Without changes	21	28
10 Years (N=74):		
Atypia	1	1.35
Relapse	1	1.35
Death	2	2.7
Without changes	4	5.4

*Intestine, lung, bone and liver. ** Endometrium and intestine. *** Brain; Locoregional. Source: IMIP (2001-2014).

DISCUSSION

In this study, a prevalence of HPV of 23.3% was evidenced in women treated for cervical adenocarcinoma, with no studies found in the researched literature. It can be said that, at the time of diagnosis, the prevalence of HPV in women with cervical carcinoma reaches 90%, one suggesting that the recommended treatment reduced the presence of the virus. It is noteworthy that there was a significant loss due to deaths, which can be explained both by the advanced age of most patients who had this outcome and by the high mortality from cervical adenocarcinoma, the fourth leading cause of cancer death in women, and high morbidity due to histological type with worse prognosis and worse response in treatment.[1] There is also a high rate of initial diagnosis above stage IIB, considered an inoperable stage.[2]

It was observed that the brown / black race, low education (equivalent <12 years of study) and low family income, following the trend seen in other studies, were the most frequent conditions in this group of women, as they are factors that predispose diagnosis delay and, consequently, a worse prognosis.[14] It was also noted that the high BMI and obesity / overweight demonstrate an important role as a risk factor for the development of some types of cancer.[15]

It is suggested in the literature that the use of illicit drugs is considered a risk factor for cervical cancer.[16] In this study, it was declared that only one patient used these substances. Low use of illicit drugs may occur due to the majority of patients presenting at an advanced age, not being frequent use in this age group, in addition to the prejudice in informing their use. Added to this risk factor is alcoholism and smoking,[17] which were also not frequent in the sample of this study. It is questioned that the sample may have been small and the study was not designed to determine the factors associated with cervical adenocarcinoma.

It is understood that the early onset of sexual activity, before the age of 14, is a risk factor associated with cervical adenocarcinoma.[17] However, in this study, an average of 18.2 years was found, not being considered early. This fact was very likely, given that the patients included were older and, in the past, sexual activity was repressed and started later. An earlier age than that found in this study, between the third and fourth decades of life, was reported as a risk factor for cervical adenocarcinoma.[18]

It was estimated that the use of Oral Hormonal Contraceptives (OHC) increases the risk by 1.9 times in relation to women who did not use it.[17] In this study, a high frequency of regular use of OHC was observed. In addition, the larger number of children also increases the incidence of cervical cancer, [17] which was similar in this study, with a median of three children. It is confirmed that the greater the number of sexual partners, the greater the risk of developing sexually transmitted infections and, consequently, HPV.[17] However, it was found that, in the women evaluated, the median was that of a partner. It is justified by the advanced age of the patients and by the customs of the past era, relating to Pap tests and colposcopy, which are important, as methods of screening for cervical cancer, for early diagnosis, as well as for treatment and better prognosis, since most women reported having undergone the preventive exam, however, without regularity. Among these, more than half of the women were found with signs of previous colposcopic invasion, representing signs of late diagnosis.

It appears that the treatment varies according to the stage and size of the lesion:[8] stages IA, IB1 and IIA, smaller than two centimeters, are various forms that vary from conization to hysterectomy with adjuvant therapy (CT + RT); and stages IIB to IVA, a group that included the majority of the patients evaluated in this study, consist of CT + RD as standard treatment with or without Brachytherapy (BT).[16] Among the evaluated patients, CT and/or RT associated or not with surgery was used as the main form of treatment chosen, which reveals the reason for the changes found in some patients after treatment, since, according to some studies, it has a favorable prognosis with surgical treatment over the years, interfering only momentarily, while RT has negative effects throughout life, which can be both a decrease in quality of life and psychological changes.[19]

Genotyping was carried out in two stages: the first, paraffin genotyping was performed at the time of diagnosis in 64 of the patients due to the lack of material at the time of collection. From these, a positive HPV result was obtained for all patients, followed by the evaluation of the most common types for the development of cancer: 16, 18, 31 and 33. In the second stage, secretion genotyping was performed after treatment for the same types, being negative for HPV in 76.7% of patients. Only one patient found a positive result for the presence of HPV, but none of the types listed above were found, so tests were performed for types 11 and 56, which were positive. The importance of this fact stands out, as the patient may have one type of HPV and, at another time, no longer have or have other associated types.

It is known that HPV type 18 is the most frequent related to cervical adenocarcinoma, however, in genotyping at the time of diagnosis of adenocarcinoma, most patients were positive for HPV type 16.[20] This difference in existing data is explained by the fact that it is a retrospective study so that some information may have been lost. It is added that another limitation was due to

the use of different HPV typing methods in diagnosis and after treatment.

After the treatment, the evolution was measured by means of routine exams and gynecological exam (colposcopy) and, in one year, an alteration was revealed in about 1/5 of the patients, which varied from death to colposcopic atypia, demonstrating there is no rule or uniformity in the changes. Metastasis or the development of another type of cancer was also described among the most serious changes, in addition to deaths.

The characteristics mentioned above are repeated after five years of treatment, with changes both in treatment sequelae, such as actinic retinitis, and by morbidity due to the patient's history. It is revealed that, in this group, for most patients, the cure criterion does not apply, as they have not completed five years after treatment or have no changes in colposcopy. Remember that, from the year of diagnosis to the year of data collection for this study, less than half (46.7%) of the patients evaluated had the equivalent of five years post-diagnosis.

It is observed that, ten years after treatment, the only changes seen were colposcopic atypia, deaths and a recurrence, repeating what was seen in other developments in which most do not apply to the cure criterion for not having clinical changes. It should also be noted that two patients in this group who died had secretion genotyping with a negative result for the types of HPV tested in this study.

Some difficulties were found in carrying out this study, mainly the loss of the sample, due to several factors, such as the difficulty of contacting them due to a change of address in relation to the medical record, due to difficult-to-access housing or the absence of patients in the hospital outpatient clinic for routine exams. Incomplete records or those that were not found at the time of data collection were added. It is believed that, fortunately, cervical adenocarcinoma is not so frequent, and this factor is a limiting factor in this study.

It is admitted that, as the study time varies from diagnosis to the date of collection of HPV genotyping by secretion, there is a variation of more than ten years and less than one year of diagnosis among patients, which may, during this period, the evaluated women had contact with the same types already presented by them or with new types. Thus, it is suggested that further studies be carried out on the persistence or not of HPV according to the types of treatment and the years after treatment, and its influence on the health of women, for a better assessment of the influence of this virus in the researched group, as well as to verify the relevance of the data obtained in this study.

CONCLUSION

In this study, the prevalence of HPV persistence of 23.3% was observed in women treated for cervical adenocarcinoma, suggesting that the recommended treatment reduced the presence of the virus. It is noteworthy that there was a significant loss due to deaths with a high rate of initial diagnosis above stage IIB.

FUNDING

Institutional Scientific Initiation Scholarship Program (PIBIC) of the National Council for Scientific and Technological Development (CNPq) of the Professor Fernando Figueira Institute of Integral Medicine (IMIP) - Recife (PE), Brazil.

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Submission: 2020/02/10
Accepted: 2020/04/03