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Profile of women with anal neoplasia associated with cervical neoplasia receiving care at a tertiary healthcare facility in northeastern Brazil



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ABSTRACT

Objective: To describe the epidemiological, clinical and laboratory profiles of women with anal neoplasia associated with cervical neoplasia attending a tertiary healthcare facility in northeastern Brazil.

Methods: This epidemiological, descriptive study was conducted using a database from a cross-sectional study carried out between December 2008 and January 2016. Women with a diagnosis of cervical neoplasia associated with anal neoplasia were included in the present study.

Results: Of the women with cervical neoplasia, 14% were found to have an anal intraepithelial lesion or anal cancer. Median age was 33 years, 68% were non-white, and 70% were from urban regions, had little schooling and low income. Most reported having had anoreceptive (73%) and unprotected intercourse (84%). Regarding symptoms, 7% reported bleeding and 11% pruritus. Overall, 10% of the sample tested positive for the human immunodeficiency virus. Anal cytology was abnormal in 92%. High-resolution anoscopy was abnormal in all cases. Histopathology revealed three cases of invasive carcinoma and high-grade lesions in 32% of the cases.

Conclusion: Women with a diagnosis of anal and cervical neoplasia are often young, non-white women, who initiated their sexual life at an early age, were exposed to unprotected anoreceptive intercourse, live in urban centers, have little schooling and a low-income level.

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Perfil de mulheres com neoplasia anal associada à neoplasia cervical atendidas em um serviço de saúde terciário do nordeste do Brasil

R E S U M O

Palavras-chave:

Infecções por papilomavírus
Neoplasia cervical
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Objetivo: Descrever os perfis epidemiológico, clínico e laboratorial de mulheres com neoplasia anal associada à neoplasia cervical atendidas em uma unidade de saúde terciária no nordeste do Brasil.

Métodos: Este estudo epidemiológico e descritivo usou um banco de dados de um estudo transversal realizado entre dezembro de 2008 e janeiro de 2016. Mulheres com diagnóstico de neoplasia cervical associada à neoplasia anal foram incluídas no presente estudo.

Resultados: Das mulheres com neoplasia cervical, 14% apresentaram lesão intra-epitelial anal ou câncer anal. A mediana de idade foi de 33 anos; 68% das pacientes não eram brancas e 70% eram provenientes de regiões urbanas, com baixa escolaridade e baixa renda. A maioria relatou histórico de relações sexuais anoreceptivas (73%) e desprotegidas (84%). Quanto aos sintomas, 7% relataram sangramento e 11% prurido. No geral, 10% das pacientes apresentaram serologia positiva para o vírus da imunodeficiência humana. A citologia anal foi anormal em 92% da amostra. A anuscopia de alta resolução foi anormal em todos os casos. A histopatologia revelou três casos de carcinoma invasivo e lesões de alto grau em 32% dos casos.

Conclusão: As mulheres com diagnóstico de neoplasia anal e cervical geralmente são jovens, não brancas, que iniciaram sua vida sexual em idade precoce, foram expostas a relações sexuais anoreceptivas desprotegidas, moram em centros urbanos e têm baixa escolaridade e baixo nível de renda.

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Introduction

Human Papillomavirus (HPV) is the agent responsible for over 90% of cases of anal and cervical cancer.¹ More than 40 HPV subtypes have tissue tropism for the anogenital tract.² The same oncogenic HPV subtypes that lead to cervical intraepithelial lesions are also associated with anal intraepithelial lesions, which are precursors of anal canal cancer.³ These subtypes of HPV act by promoting the development of lesions in the transitional zone in the junctional epithelium of the anal canal.⁴

Despite being one of the less common forms of gastrointestinal cancer, the attention paid to anal and anal canal cancer has increased over recent decades due to the rise in their incidence, particularly in women.⁵ Around 8000 new cases of anal cancer were estimated to occur in the United States in 2015, with the frequency being higher among women compared to men.⁶ Furthermore, estimates indicate that over 34,000 new cases of HPV-associated anal intraepithelial neoplasia occur each year.⁷

The incidence of precursor lesions and squamous cell carcinoma of the anus is highest among HIV-positive individuals and men who have sex with men. However, for these groups, guidelines for anal dysplasia screening are already in place.⁸ On the other hand, women with genital neoplasia, solid organ transplantation recipients and individuals submitted to chronic immunosuppression for various diseases are also at a significantly increased risk of neoplastic precursor lesions of the anal canal.^{9,10} Consequently, screening for precursor

lesions has been encouraged in these groups.¹¹⁻¹³ Nevertheless, there is a need for further investigation into the profile of the women affected by this disease, since few studies have been conducted in this population.

The objective of the present study was to describe the epidemiological, clinical and laboratory profile of women with anal neoplasia associated with cervical neoplasia attending a tertiary healthcare facility in Recife, Pernambuco, a state of northeastern Brazil.

Methods

A descriptive, epidemiological study was conducted based on a database from a cross-sectional, observational study conducted between December 2008 and January 2016. The original study included all the women attending the lower genital tract pathology outpatient department of the *Instituto de Medicina Integral Prof. Fernando Figueira* (IMIP) with a histopathology diagnosis of cervical intraepithelial neoplasia or cervical cancer. Women undergoing radiotherapy or chemotherapy were excluded from the study, as well as those suffering from mental illness, incarcerated women and those known to be HIV-positive.

The women who fulfilled all the eligibility criteria were included in the study if they voluntarily agreed to participate and signed an informed consent form. The institute's internal review board approved the protocol of the original study under reference number CAAE 0230.0.099.000-11.

The participants answered an epidemiological questionnaire, underwent gynecological examination and were screened for Sexually Transmitted Infections (STIs). An Enzyme-Linked Immunosorbent Assay (ELISA) was used to test for HIV, VDRL was used to test for syphilis, and antibody testing was conducted for hepatitis B and C. In addition, brush specimens were collected for anal cytology, High-Resolution Anoscopy (HRA) was performed, and biopsy was carried out whenever indicated. The same professional performed all the procedures throughout the entire study period.

Anal cytology was conducted using an endocervical brush moistened in saline solution and introduced up to 4 cm from the anal verge. The slides were fixed in 96% ethanol, stained using the Papanicolaou technique and classified according to the Bethesda system terminology.¹⁴

HRA was performed following inspection of the perianal region, digital rectal examination, anoscopy and application of 5% acetic acid and Lugol's iodine solution, with colposcopic evaluation of the transitional zone of the anal canal. The classification used was that of the Brazilian Association of Genitoscopy (Barcelona Consensus, 2002).¹⁵ The lesions identified at HRA were biopsied in the clinic under local anesthesia, except for lesions associated with large prolapsed hemorrhoids, which were managed by a proctologist.

Results

A total of 1242 women with a histopathological diagnosis of cervical intraepithelial neoplasia or cervical cancer were screened for anal intraepithelial lesions. Of these, 14% ($n = 181$) were diagnosed with anal intraepithelial neoplasia or anal cancer. In relation to the biological and sociodemographic characteristics of this subgroup, 56% were over 35 years of age, with a median age of 33 years (range 16–75 years); 68% were non-white; the majority (72%) lived in an urban center and 70% reported a family income of no more than one minimum salary. Median education level consisted of 6 years of schooling (range 0–13 years), with 63% of the women in the study having between 0 and 7 years of schooling (Table 1).

Regarding their sexual, reproductive and behavioral characteristics, median age at sexual debut was 16 years (range 8–30 years); 73% reported having had anoreceptive intercourse and most reported having first had anal intercourse before completing 30 years of age. Few used condoms (16%) and only 11% reported having had genital warts. Median parity was 2 (range 0–9) (Table 2).

Proctologic diseases in general were present in 69% of cases. Anal skin tags were the most common finding (63%) followed by hemorrhoids (26%). Anal bleeding was reported by 7% of the women and pruritus by 11%. ELISA for HIV was positive in 10% of the patients, while VDRL was positive in 2%. None of the women tested positive for hepatitis B or C (Table 3).

Regarding the results of the anal Pap smears, 92% were abnormal, consisting of atypical squamous cells of undetermined significance in 15%, low-grade intraepithelial lesions in 53% and high-grade intraepithelial lesions in 24%. HRA was abnormal in all cases, with acetowhite epithelium being found in 89% of cases and constituting the most common abnormality. Histopathology revealed HPV infection in 25% of cases,

Table 1 – Biological and sociodemographic characteristics of the women with cervical and anal neoplasia ($n = 181$).

Characteristics	n	%
<i>Age</i>		
0–35 years	79	43.6
≥36 years	102	56.4
<i>Skin color</i>		
White	58	32.0
Non-white	123	68.0
<i>Family income</i>		
≤1 minimum salary	126	69.6
>1 minimum salary	55	30.4
<i>Schooling</i>		
0–7 years	114	63.0
≥8 years	67	37.0
<i>Area of residence</i>		
Rural	51	28.2
Urban	130	71.8
<i>Marital status</i>		
With a stable partner	100	55.2
No stable partner	81	44.8

Table 2 – Sexual, reproductive and behavioral characteristics of the women with cervical and anal neoplasia ($n = 181$).

Characteristics	n	%
<i>Age at first sexual intercourse</i>		
≤16 years	91	50.3
≥17 years	90	49.7
<i>Number of partners</i>		
1–4	117	64.6
≥5	64	35.4
<i>Anal intercourse</i>		
Yes	132	72.9
No	49	27.1
<i>Age at first anal intercourse ($n = 132$)</i>		
≤30 years	115	87.1
≥31 years	17	12.9
<i>History of genital warts</i>		
Yes	20	11.0
No	161	89.0
<i>Use of the oral contraceptive pill</i>		
Yes	59	32.6
No	122	67.4
<i>Use of condoms</i>		
Yes	29	16.0
No	152	84.0
<i>Parity</i>		
0–2	109	60.2
≥3	72	39.8
<i>Smoker</i>		
Yes	41	22.7
No	140	77.3
<i>Consumes alcohol</i>		
Yes	79	43.6
No	102	56.4

Table 3 – Clinical and laboratory characteristics of the women with cervical and anal neoplasia (n = 181).

Characteristics	n	%
Anal disorders		
Yes	124	68.5
No	57	31.5
Hemorrhoids		
Yes	47	26.0
No	134	74.0
Anal skin tag		
Yes	114	63.0
No	67	37.0
Anal fissure		
Yes	2	1.1
No	179	98.9
Fistula		
Yes	0	0
No	181	100
Bleeding		
Yes	12	6.7
No	164	90.6
Data missing	5	2.7
Pruritus		
Yes	19	10.5
No	157	86.8
Data missing	5	2.8
ELISA for HIV		
Positive	18	9.9
Negative	163	90.1
VDRL		
Yes	3	1.6
No	177	97.8
Not performed	1	0.6
Hepatitis B and C		
Positive	0	0
Negative	179	98.9
Not performed	2	1.1

low-grade intraepithelial lesion in 41%, high-grade intraepithelial lesion in 32% and three cases of invasive carcinoma (Table 4).

Discussion

The present sample of women with anal and genital neoplasia consisted mainly of young, poor, non-white women with little schooling, living in urban centers. This profile resembles that of users of the Brazilian National Health Service in this region and reflects the degree of social inequality that exists in our urban centers,¹⁶ a fact that has also been reported in other studies.^{17,18} These are women who begin their sexual life at an early age and who have unprotected sex, including unprotected anal intercourse.¹⁸⁻²⁰ Because HPV infection is an STI, unprotected sex is a risk factor for HPV infection, which in turn increases the risk of an invasive lesion both in the female genital organs and in the anal canal.²⁰ The population in general should be made aware of this fact, and women, in particular, should be empowered, since those in

Table 4 – Frequency distribution of the anal cytology, colposcopy and histopathology results (n = 181).

Cytology	n	%
Within normal parameters	13	7.2
Atypical squamous cells of undetermined significance	27	14.9
Low-grade intraepithelial lesion	96	53.0
High-grade intraepithelial lesion	44	24.3
Unsatisfactory	1	0.6
High-resolution anoscopy		
Acetowhite epithelium	162	89.5
Mosaic	2	1.1
Punctation	1	0.6
Verrucous lesions	5	2.8
Association of images	11	6.1
Anal histopathology		
HPV infection	46	25.4
Anal intraepithelial neoplasia grade 1	75	41.4
Anal intraepithelial neoplasia grade 2	34	18.8
Anal intraepithelial neoplasia grade 3	23	12.7
Invasive carcinoma	3	1.7

situations of greater vulnerability often find it difficult to negotiate condom use with their partner.

The high levels of alcohol consumption and smoking (44% and 23%, respectively) found here are factors that have already been reported as being associated with the development of neoplasia.²¹ Public health policies aimed at reducing and controlling smoking and alcohol consumption do exist. The prevention of various neoplasms, including HPV-associated neoplasia, should be at the core of these programs.

Symptoms such as bleeding, pruritus and even anal pain are present in only around 15% of cases of anal neoplasia, irrespective of sex, sexual habits or the grade of the lesion found.²² All of these symptoms except for anal pain were reported in the present study. Nevertheless, since such lesions are often asymptomatic, consideration is being given to proposing new ways of alerting the population and to making screening broader-reaching and effective, particularly for higher-risk groups such as women with cervical intraepithelial lesions and invasive cervical cancer.

STIs such as *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, syphilis, herpes simplex virus 2 and HPV have been shown to play an important role in the acquisition of HIV.²³ This evidence supports the recommendation to test women with an HPV infection for other STIs, particularly HIV and syphilis. In this sample of women, 10% tested positive for HIV, a fact previously unknown, since a prior diagnosis of HIV was one of the exclusion criteria established for this study. Because this population has been found to be vulnerable, the practice has now been adopted in this institute to routinely investigate for STIs.

Anal cytology screening is the most common method used to screen for anal cancer precursor lesions in high-risk individuals, with an effectiveness that is similar to that found for cervical cytology.⁸ The sensitivity of anal cytology ranges from 42% to 98%, with specificity of 32% to 96%.²⁴ As expected, the majority of cytology tests were abnormal in the sample investigated in the present study, since this was a subgroup of patients with anal lesions. However, these results suggest

that anal cytology is sensitive enough for the detection of HPV-induced anal lesions in women with cervical neoplasia.

Cytology screening identifies those patients, in whom a further, more detailed investigation is warranted, contributing toward the early diagnosis and treatment of precursor lesions. Considering the substantial reduction in cervical cancer-associated morbidity and mortality in developed countries following the implementation of population-based screening programs^{25,26} and bearing in mind the similarities that exist between the cervix and the anal canal,⁴ it is reasonable to assume that screening programs for anal neoplasia in risk groups could reduce the incidence of anal cancer and increase survival rates as a function of early diagnosis and treatment.

Histopathology revealed that HPV-related lesions and low-grade lesions, respectively, were the most common findings; however, 30% of cases consisted of high-grade lesions and there were three cases of invasive cancer. Therefore, screening for anal lesions in patients with cervical intraepithelial neoplasia or cervical cancer is crucial for preventing progression to invasive squamous cell carcinoma, since prognosis is inversely proportional to staging at the time of diagnosis.²⁷

These results serve to reinforce the need for further studies in the country on this subject and to highlight the importance of systematic screening for anal lesions in women with cervical neoplasia,²⁴ which should be incorporated into the Brazilian government's national policy for women's comprehensive healthcare.²⁸ In addition, these findings emphasize the magnitude of the problem of HPV infection, including the potential development of anal intraepithelial lesions and anal cancer, and should serve to encourage health departments to increase the number of awareness campaigns and HPV vaccination programs.

Conclusion

Women with a diagnosis of anal neoplasia associated with cervical neoplasia are often young, non-white women living in urban centers, with low incomes and poor schooling. They begin their sexual life early, have anoreceptive sex and do not use condoms. They come from regions where the availability of public services is often deficient. In view of these characteristics, these are the women who would benefit most from educational measures, vaccination and early screening for anal lesions.

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Conflicts of interest

The authors declare no conflicts of interest.

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REFERENCES

1. Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. American Cancer Society American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin.* 2012;62:147–72.
2. de Lima Júnior SF, Fernandes MC, Heráclio SA, de Souza PR, Maia MM. Prevalence of human papillomavirus genotypes: comparison between three detection methods in patients from Pernambuco, Brazil. *Rev Bras Ginecol Obstet.* 2011;33:315–20.
3. Zbar AP, Fenger C, Efron J, Beer-Gabel M, Wexner SD. The pathology and molecular biology of anal intraepithelial neoplasia: comparisons with cervical and vulvar intraepithelial carcinoma. *Int J Colorectal Dis.* 2002;17:203–15.
4. Yang EJ, Quick MC, Hanamornroongruang S, Lai K, Doyle LA, McKeon FD, et al. Microanatomy of the cervical and anorectal squamocolumnar junctions: a proposed model for anatomical differences in HPV-related cancer risk. *Mod Pathol.* 2015;28:994–1000.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin.* 2016;66:7–30.
6. Dunne EF, Markowitz LE, Saraiya M, Stokley S, Middleman A, Unger ER, et al. Centers for Disease Control and Prevention (CDC) CDC grand rounds: reducing the burden of HPV-associated cancer and disease. *MMWR Morb Mortal Wkly Rep.* 2014;63:69–72.
7. Viens LJ, Henley SJ, Watson M, Markowitz LE, Thomas CC, Thompson TD, et al. Human papillomavirus-associated cancers – United States, 2008–2012. *MMWR Morb Mortal Wkly Rep.* 2016;65:661–6.
8. Patel J, Salit IE, Berry MJ, de Pokomandy A, Nathan M, Fishman F, et al. Environmental scan of anal cancer screening practices: worldwide survey results. *Cancer Med.* 2014;3:1052–61.
9. Leeds IL, Fang SH. Anal cancer and intraepithelial neoplasia screening: a review. *World J Gastrointest Surg.* 2016;8:41–51.
10. Moscicki AB, Darragh TM, Berry-Lawhorn JM, Roberts JM, Khan MJ, Boardman LA, et al. Screening for anal cancer in women. *J Low Genit Tract Dis.* 2015;19 Suppl. 1:S27–42.
11. Nahas CS, Da Silva Filho EV, Segurado AA, Genevcius RF, Gerhard R, Gutierrez EB, et al. Screening anal dysplasia in HIV-infected patients: is there an agreement between anal pap smear and high-resolution anoscopy-guided biopsy? *Dis Colon Rectum.* 2009;52:1854–60.
12. Nadal SR, Manzione CR. Screening and follow-up of patients with anal HPV induced lesions for anal carcinoma prevention. *Rev Bras Colo-Proctol.* 2009;29:250–3.
13. Heráclio SA, Schettini J, Oliveira ML, Souza AS, Souza PR, Amorim MM. High-resolution anoscopy in women with cervical neoplasia. *Int J Gynecol Obstet.* 2015;128:216–9.
14. Apgar BS, Zoschnick L, Wright TC Jr. The 2001 Bethesda System terminology. *Am Fam Phys.* 2003;68:1992–8.
15. Bornstein J, Bentley J, Bösze P, Girardi F, Haefner H, Menton M, et al. 2011 colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy. *Obstet Gynecol.* 2012;120:166–72.
16. Informações socioeconômicas. Prefeitura do Recife [Internet]. [Socioeconomic data. Recife City Hall]. Available from: <http://www2.recife.pe.gov.br/pagina/informacoes-socioeconomicas> [accessed 05.08.18].
17. Celie KB, Jackson C, Agrawal S, Dodhia C, Guzman C, Kaufman T, et al. Socioeconomic and gender disparities in anal cancer diagnosis and treatment. *Surg Oncol.* 2017;26:212–7.

18. Lin D, Gold HT, Schreiber D, Leichman LP, Sherman SE, Becker DJ. Impact of socioeconomic status on survival for patients with anal cancer. *Cancer*. 2018;124:1791-7.
19. Capobiango A, Silva Filho AL, Nunes TA. Anal HPV diagnosis in women with NIC: anal cancer prevention? *Rev Bras Colo-Proctol*. 2009;29:443-50.
20. ElNaggar AC, Santoso JT. Risk factors for anal intraepithelial neoplasia in women with genital dysplasia. *Obstet Gynecol*. 2013;122:218-23.
21. Grulich AE, Poynten IM, Machalek DA, Jin F, Templeton DJ, Hillman RJ. The epidemiology of anal cancer. *Sex Health*. 2012;9:504-8.
22. Hicks CW, Wick EC, Leeds IL, Efron JE, Gearhart SL, Safar B, et al. Patient symptomatology in anal dysplasia. *JAMA Surg*. 2015;150:563-9.
23. Boily MC, Baggaley RF, Wang L, Masse B, White RG, Hayes RJ, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. *Lancet Infect Dis*. 2009;9:118-29.
24. Cronin B, Bregar A, Luis C, Schechter S, Disilvestro P, Pisharodi L, et al. Evaluation of anal cytology and dysplasia in women with a history of lower genital tract dysplasia and malignancy. *Gynecol Oncol*. 2016;141:492-6.
25. Benard VB, Thomas CC, King J, Massetti GM, Doria-Rose VP, Saraiya M, et al. Centers for Disease Control and Prevention (CDC) Vital signs: cervical cancer incidence, mortality, and screening – United States, 2007–2012. *MMWR Morb Mortal Wkly Rep*. 2014;63:1004-9.
26. Lantz PM, Mullen J. The National Breast and Cervical Cancer Early Detection Program: 25 years of public health service to low-income women. *Cancer Causes Control*. 2015;26:653-6.
27. Johnson LG, Madeleine MM, Newcomer LM, Schwartz SM, Daling JR. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973–2000. *Cancer*. 2004;101:281-8.
28. Xavier de Castro L, Simonetti MC, Araújo MJ. Monitoramento e acompanhamento da política nacional de atenção integral à saúde da mulher e do plano nacional de políticas para as mulheres [Monitoring and follow-up of the national policy on comprehensive healthcare for women and the national policy plan for women]. Brasília, DF: Ministério da Saúde; 2015.