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Prevalence and risk factors for anal intraepithelial neoplasia in patients with high- grade cervical intraepithelial lesion.

Prevalencia y factores de riesgo de la neoplasia intraepitelial anal en pacientes con lesión intraepitelial cervical de alto grado

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Abastract

OBJECTIVE: To determine the prevalence of alterations in anal cytology, anal human papillomavirus infection, and anal intraepithelial neoplasia. Also, to explore the risk factors and associated serotypes in patients with high-grade cervical intraepithelial lesion, based on the hypothesis that this population is at higher risk for precancerous lesions or anal cancer.

MATERIALS AND METHODS: Observational, descriptive, cross-sectional study, with analytical component, performed in patients diagnosed with high-grade cervical intraepithelial lesion (HG-CIL) at two health institutions in Bogota: one private and one public, seen between January 2017 and February 2018. A non-probabilistic sampling was performed, by convenience, with a calculated sample of 124 patients.

RESULTS: One hundred nineteen participants were included, 4 of them showed evidence of abnormal cells in the anal cytology, in the tissue lining the outside of the cervix. Fourteen abnormal anoscopies were found, with a prevalence of anal intraepithelial neoplasia of 6.7%. Seven were low-grade anal intraepithelial neoplasia and one was high-grade. Anal human papillomavirus (HPV) infection was detected in 45 participants (37.8%) and high-risk HPV (HR-HPV) genotypes were detected in 29 participants (24.4%). Having more than 3 sexual partners, more than 3 children and being younger than 21 years before first pregnancy had a p-value < 0.05, leading to an increased risk of anal HPV infection.

CONCLUSION: It is important to establish protocols in Colombia for the detection of anal intraepithelial neoplasia in high-risk groups, such as patients with cervical intraepithelial neoplasia or cervical cancer, and to promote training in high-resolution anoscopy in specializations related to the diagnosis of anogenital pathology.

KEYWORDS: Papillomavirus infection; Uterine cervical neoplasms; Cervix; Cytology, Sexual partners; Uterine cervical dysplasia; Anus neoplasms; Genotype.

Resumen

OBJETIVO: Determinar la prevalencia de alteraciones en la citología anal, infección anal por virus del papiloma humano y en la neoplasia intraepitelial anal; además, explorar los factores de riesgo y los serotipos asociados en pacientes con lesión intraepitelial cervical de alto grado, a partir de la hipótesis de que esta población tiene mayor riesgo de lesiones precursoras o cáncer anal.

MATERIALES Y MÉTODOS: Estudio observacional, descriptivo y transversal, con componente analítico, efectuado en pacientes con diagnóstico de lesión intraepitelial cervical de alto grado (LIEAG) en dos instituciones de salud: una privada y otra pública

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de Bogotá, atendidas entre enero de 2017 y febrero de 2018. Se efectuó un muestreo no probabilístico, por conveniencia, con una muestra calculada en 124 pacientes.

RESULTADOS: Se incluyeron 119 participantes, en 4 de ellas se evidenció, en la citología anal, el hallazgo de células anormales en el tejido que reviste la parte exterior del cuello uterino. Se encontraron 14 anoscopias anormales que dieron una prevalencia de neoplasia intraepitelial anal del 6.7%. Siete eran neoplasia intraepitelial anal de bajo grado y una de alto grado. Se encontró infección por VPH anal en 45 participantes (37.8%) y se detectaron genotipos de VPH-AR en 29 participantes (24.4%). Más de 3 compañeros sexuales, más de 3 hijos y tener menos de 21 años antes del primer embarazo tuvieron un valor de $p < 0.05$ que confiere mayor riesgo de infección por VPH anal.

CONCLUSIÓN: Es importante establecer en Colombia protocolos para la detección de la neoplasia intraepitelial anal en grupos de alto riesgo, como las pacientes con neoplasia intraepitelial cervical o cáncer de cuello uterino, e incentivar el adiestramiento en la anoscopia de alta resolución de especialidades relacionadas con el diagnóstico de patología anogenital.

PALABRAS CLAVE: Infección por papilomavirus; neoplasias cervicales uterinas; cuello uterino; citología; parejas sexuales; displasia cervical uterina; neoplasias del ano; genotipo.

BACKGROUND

Anal cancer is uncommon, but its incidence has risen, especially in industrialized countries.[1] Globally, in the year 2020, there were 50,865 cases,[2] 5,347 in Latin America and the Caribbean,[3] and 483 in Colombia.[4] This type of cancer is more common in women,[5,6] and 80 to 90% of the cases are associated with high-risk human papillomavirus persistent infections (HR-HPV).[6,7] Previously, HPV-16 was thought to be a main factor for anal cancer and its precursor lesion,[8,9] however, HR-HPV other than HPV-16 and 18 have been identified.[10,11]

Besides having a similar natural history to that of cervix cancer,[5] patients with grade 2 or 3 cervical intraepithelial neoplasia (CIN) are at higher risk of anal cancer.[12,13] This higher risk has been observed in incidence rates of 1.82 to 6.3 in women with a history of cervical cancer, and 4.2 to 16.4 in women with a history of CIN3.[14] Regardless of the age at the time of diagnosis, a history of CIN2 increases the risk of anal cancer (OR 2.9; CI95%: 2.0-4.1), and CIN3 represents a higher relative risk (OR 4.8; CI95%: 3.3-7.0). This higher risk remains up to 25 years after diagnosis.[15] A history of CIN3 has a RR of 4.03 (CI 95%: 2.59-6.28) for anal cancer[7], and an incidence rate ratio of 6.68 (CI 95%: 3.64-12.25) for anal intraepithelial neoplasia grade 3 (AIN3).[16]

Anal cancer shares risk factors with cervical cancer: immunosuppression secondary to HIV infection, or solid organ transplantation, smoking, and more than three sexual partners in lifetime.[6,17,18] Other associated risk factors are nulliparity,[7] and a history of anal fistulas, among others.[17,19] The age of initiation of sexual relations, and the age of first birth are subjects of the present study, to determine if they can be considered risk factors or not.[20]

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The ANCHOR[17] study sought to determine if the treatment for AIN was effective to reduce the progression to anal cancer in patients with HIV infection. While the sample included men and women (women were 18.9% of the universe), it is important to note that the female patients who received treatment for AIN had a progression to anal cancer rate 57% lower than the active follow-up group. Thus, this cancer is potentially susceptible of being prevented if the precursor lesion is treated. However, it is often diagnosed late due to a lack of early detection measures, leading to a limited survival rate.[17] Due to the aforementioned, the goal of the study was to determine the prevalence of alterations in anal cytology, anal infection with human papillomavirus, and anal intraepithelial neoplasia, and also to explore risk factors and associated serotypes in patients with high-grade cervical intraepithelial lesion, based on the hypothesis that this population has a higher risk of precursor lesions, or anal cancer.

MATERIALS AND METHODS

Observational, descriptive, cross-sectional study, with an analytical component, carried out with patients with a diagnosis of high-grade cervical intraepithelial lesion (HG-CIL) in two health institutions in Bogota, one private and one public. The patients were seen between January 2017 and February 2018. A non-probabilistic, convenience sample was made, calculated for 124 patients. *Inclusion criteria*: women between 21 and 65 years seen in consultation for cervical pathology and colposcopy, with a diagnosis of high-grade cervical intraepithelial lesion, or in situ carcinoma, who accepted to participate in the study. *Exclusion criteria*: pregnant women, inability to sign the informed consent, and rejection of anoscopy. *Procedure*: Upon signing the informed consent, sociodemographic and clinical characteristics were gathered with a questionnaire. The anal sample for cytology and typification of HR-HPV was taken in gynecological position, with the insertion of a Cytobrush, 3 to 4 cm in the anal canal, rotated 360°, applying pressure to the walls, between 5 to 10 times. The labelled sample was stored at 4°C in the laboratory.

All the cytology tests were processed by a cyto-technician, who reported the results in compliance to the Bethesda 2014 system,[21] which classifies lesions as: ASCUS, low grade (AIN1), high grade (AIN2/3), and in situ cancer. Positive results were reviewed, and every ten cytologies went through the pathologist's quality control.

The human papillomavirus genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 were identified by PCR in real time (Cobas® 4800 [Roche]). The human beta-globin gene was used to verify the reaction, and the procedures were performed in accordance with the manufacturer's instructions.

The high resolution anoscopy was made with a Soundmed Colpo-99 Plus colposcope, and a Premier Medical disposable Uniscope anoscope. The participants were in Sims' position (semi-prone), and water-based lubricant was used for inserting the anoscope. A brush covered with gauze and soaked in acetic acid at 3% was then introduced, and the anoscope was removed, leaving the brush in contact with the rectal walls for 1 minute. The gauze-covered brush was then removed, and the anoscope was inserted, to visualize, through the colposcope, the areas which were compatible with intra-anal lesion. When evidence was found, a biopsy was made with a bioptome of 0.3 mm, after regional anesthesia. The labelled samples were kept in a container with formaldehyde at 10%, transported to the laboratory where they were processed and analyzed by pathologists. Anal intraepithelial neoplasia positive results were checked by another pathologist.

The collection of samples and anoscopies was made by one of the researchers, certified by the

Mexican Colposcopy and Oncology Society. The data was captured directly by two of the researchers, and all doubts were cleared by another researcher, according to medical history records. The samples were delivered immediately to the laboratory. The bacteriologists and pathologists who processed the samples were blind to the results of the anoscopies.

All patients received a written report with its corresponding advisory to explain the results. Abnormal findings were informed, and they were referred to the corresponding department for treatment.

Included variables: age, smoking (considered positive if the patient had smoked in the last 10 years), age of initiation of sexual relations, parity, age at first childbirth, history of receptive anal sex, and number of sexual partners.

The categorical variables were summarized as frequencies (absolute and relative), and continuous ones as median and interquartile range (IQR). The frequency of anal human papillomavirus, abnormal cytology, and anal intraepithelial neoplasia were measured. Quantitative ordinal and nominal variables were described with proportions. After the normality Kolmogorov-Smirnov test, an abnormal distribution of continuous variables was found, so they are described as medians and IQR. For the bivariate analysis, the differences between sub-groups were evaluated, and ratios of verisimilitude (odds ratio; OR) were calculated, to explore risk factors associated with the anal human papillomavirus, and anal intraepithelial neoplasia. A value of $p < 0.05$ was considered statistically significant. The statistical analyses were processed with STATA 15 software.

The study was approved by the Committee of Ethics of the *Universidad de La Sabana*, and it was financed by the research group of this University. The authors declare no conflict of interests.

RESULTS

One hundred nineteen patients were included, 4 of them showed evidence, in anal cytology, of abnormal cells in the tissue lining the outer part of the cervix (ASCUS); 14 anoscopies were abnormal, so anal biopsies of these patients were taken, resulting in an anal intraepithelial neoplasia prevalence of 6.7% (CI 95%: 3.2-12.3). **(Figure 1)** Out of the 119 participants, 33 (27.7%) had CIN2, 78 (65.5%) CIN3, and 8 (6.7%) in situ carcinoma. No participants were lost during the follow-up.

Table 1 shows the findings related with the studied variables. The obtained medians were age: 38 (IQR: 32-44), age of initiation of sexual relations: 17 (IQR: 15-19), sexual partners: 3 (IQR: 2-4), and parity: 2 (IQR: 1-3) children. Smoking was identified in 13.5%, and anal intercourse in 60 participants (50.4%).

The anal cytology was unsatisfactory in 2 participants, due to squamous enucleated cells that hindered evaluation. Out of 117 cytologies, 4 were positive to ASCUS. 14 anoscopies were abnormal, so an anal biopsy was taken from these patients, resulting in a prevalence of 6.7% (CI: 95%: 3.2-12.3) for anal intraepithelial neoplasia. Seven of these cases were low-grade, and one was high-grade.

We found human papillomavirus infection in 45 participants (37.8%), and a HR-HPV genotype was identified in 29 participants (24.4%). Six participants (5.0%) had HPV-16 with other HR-HPV, and 3 participants (2.5%) had HPV-18 with other HR-HPV. The patient who had high-grade anal intraepithelial neoplasia, had HPV-16 with other HR-HPV (OR: 3.02; CI 95%: 0.31-29.59; p: 0.314). For the patients who presented with low-grade anal intraepithelial neoplasia, 3 had genotypes other than HR-HPV 16 and 18, (OR: 2.17; CI 95%: 0.51-1.60; p: 0.929), and for the rest of them, the genotype was reported as negative.

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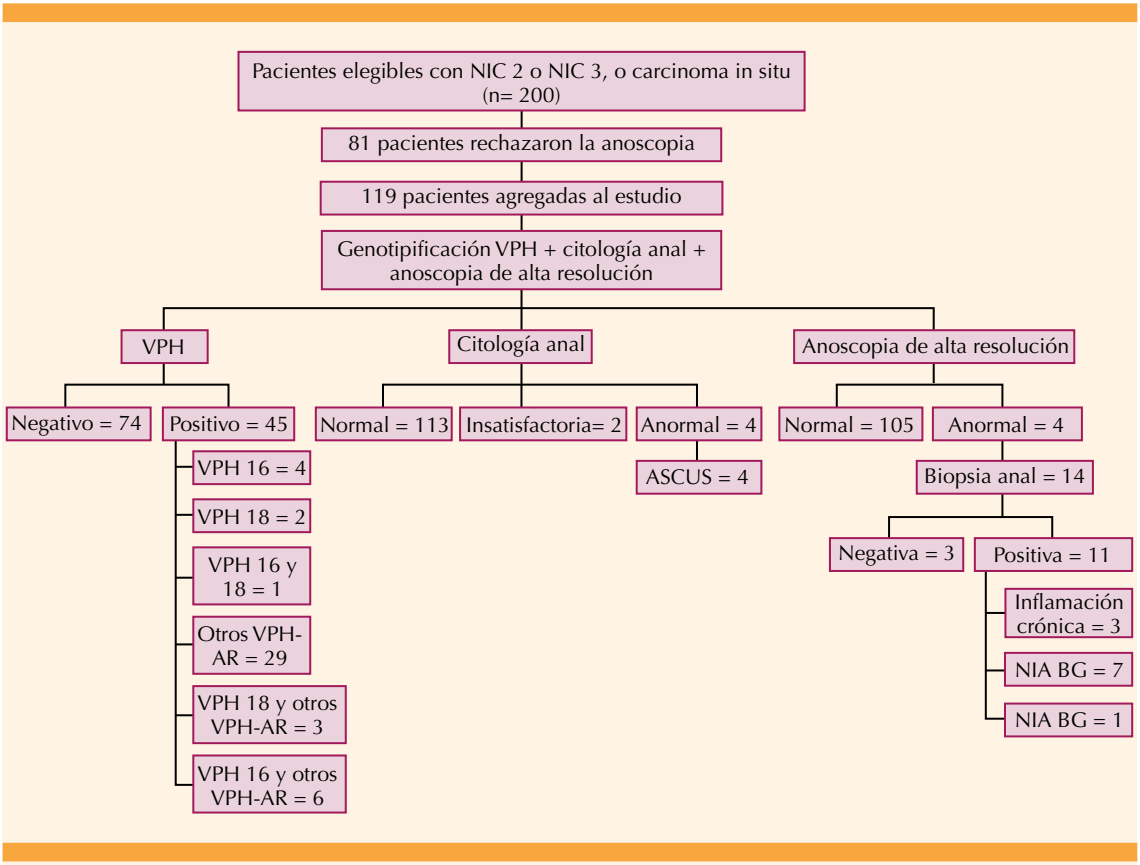


Figure 1. Participant distribution.
CIN: cervical intraepithelial neoplasia, HPV: human papillomavirus, LG-AIN: low-grade anal intraepithelial neoplasia, HG AIN: high-grade anal intraepithelial neoplasia.

Table 1. Studied variables

Variable	Median (IQR)
Age (years)	38 (32-44)
Age of initiation of sexual relations	17 (15-19)
Sexual partners	3 (2-4)
Children	2 (1-3)
Age at first childbirth	20 (17-22)
	n (%)
Smoking	16 (13.5)
Anal intercourse	60 (50.4)

IQR: interquartile range, n: sample.

Bivariate analysis: The risk factors for anal infection due to HPV, and anal intraepithelial neoplasia are shown in Tables 2 and 3. A higher number of sexual partners than 3, parity higher than 3 children, and age at first childbirth lower than 21, had a p value < 0.05, leading to higher risk of infection with anal HPV. The association between risk factors and anal intraepithelial neoplasia was not statistically significant.

DISCUSSION

The prevalence for anal intraepithelial neoplasia in the present study was 6.7%, while the preva-

lence reported in the literature is 12.2% (CI 95%: 8-17) for patients with genital intraepithelial neoplasia,[22] and CIN2, or greater in 0 to 9% of women with lower genital tract pathology.[23]

Anal HPV was evident in 37.8% of the participants, identifying HPV-16, HPV-18, and other HR-HPV. This is in agreement with the relevant literature, where out of 28% of women with high-grade cervical dysplasia, 78% of them had HR-HPV other than HPV-16 (26%), and HPV-18 (7%).[11] Another study evaluated the rate of cervical, anal, and oral human papillomavirus detection, in women referred to colposcopy with a report of HR-HPV in 54.2% of them, the one most frequently detected was HPV-53, followed by HPV-31, HPV-51, and HPV-16.[10]

The cytology alterations in the studied population were of 3.3%, very similar to the report of Sanchez et al.[24] in Colombia, who sought to establish the prevalence of anal infection by HR-HPV, and abnormal anal cytology in women with cervical dysplasia. They found that 32% of 100 patients had HR-HPV infection, and 68.8% had genotypes other than HPV-16 and 18. These authors reported a prevalence of abnormal anal cytology of 2.8%. However, they included patients with low-grade intraepithelial lesion diagnosis, and didn't establish histology diagnosis of anal pathology.

Of the risk factors for anal human papillomavirus, the number of sexual partners higher than 3, parity higher than 3, and age at first birth lower than 21 years, had a p value of < 0.05, meaning higher risk. While there was no statistical significance in the association between risk factors and anal intraepithelial neoplasia, the literature highlights a higher risk of anal cancer with a significant trend between a higher number of sexual partners of the opposite sex (with a p value of < 0.001[25]), and a history of receptive anal intercourse, especially before 30 years old, leading to higher risk (OR: 3.4; CI 95%: 1.7-6.7).[25] The risk of anal cancer is greater in premenopausal women with active smoking (OR: 5.6; CI 95%: 2.4-12.7),[26] and there is a linear increase of the risk, the higher the number of cigarettes per day, and years of smoking.[27]

Table 2. Anal human papillomavirus risk factors

Risk factor		n	n HPV + (%)	OR (CI 95%)	p
Sexual partners	1 - 2	39	12 (30.7)	2.31 (1.08-4.92)	0.03
	More than 3	80	33 (41)		
Smoking	Yes	16	9 (56.2)	2.39 (0.82-6.96)	0.10
	No	103	34 (33)		
Anal intercourse	Yes	60	25 (41.6)	1.39 (0.66-2.93)	0.83
	No	59	20 (33.8)		
Parity	0 - 2	76	34 (44.7)	0.42 (0.19-0.96)	0.04
	More than 3	43	11 (25.5)		
Initiation of sexual relations	Less than 17 years	54	16 (29.6)	0.76 (0.35-1.61)	0.09
	More than 17 years	65	29 (44.6)		
Age at first childbirth	Less than 21 years	41	11 (26.8)	1.07 (1.01-1.15)	0.02
	More than 21 years	78	34 (43.5)		

HPV: human papillomavirus; OR: odds ratio; CI: confidence interval.

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Table 3. Risk factors for anal intraepithelial neoplasia

Risk factor		n	n HPV + (%)	OR (CI 95%)	p
Number of sexual partners	1 a 2	39	1 (2.5)	3.61 (0.53-84.7)	0.23
	> 3	80	7 (8.7)		
Smoking	Yes	16	3 (18.7)	4.43 (0.79-21.5)	0.08
	No	103	5 (4.8)		
Anal intercourse	Yes	60	5 (8.3)	1.69 (0.37-8.9)	0.50
	No	59	3 (5.0)		
Parity	0 a 2	76	7 (9.2)	0.23 (0.01-1.6)	0.16
	> 3	43	1 (2.3)		
Initiation of sexual relations	<17*	54	2 (3.7)	0.38 (0.05-1.88)	0.25
	>17*	65	6 (9.2)		
Age at first childbirth	<21*	41	3 (7.3)	1.51 (0.21-5.25)	0.83
	>21*	78	5 (6.4)		
Anal HPV	Positive	45	4 (8.8)	1.69 (0.36-7.90)	0.48
	Negative	74	4 (5.4)		

**Years, HPV: Human papillomavirus, OR:* Odds-ratio, CI: Confidence interval.

Given that the absolute risk of anal cancer at 5 years in patients with a CIN3 diagnosis is of 14.1%, and 3.2% in the HIV positive, and negative population, respectively,[28] in the context of a cancer that is susceptible of prevention by treating precursor lesions, it is relevant, that out of 119 patients with high-grade intraepithelial cervical lesion, or in situ cancer, only one patient with high-grade anal intraepithelial neoplasia was found. In Colombia, the current screening recommendations for anal cytology are limited to patients with a history of anal intercourse, or who had perianal infection by human papillomavirus,[29] without specification of which patients require genotype determination of the anal human papillomavirus. Anoscopy is a high-cost detection tool, limited availability,[17] and significant unawareness of its use in Colombia.[30]

The strengths of the present study are that it is the first, to this date, in Colombia, to establish the prevalence of alterations in anal cytology, anal infection by HPV, and of anal intraepithelial neoplasia, while also exploring the risk factors and associated serotypes in patients with high-grade cervical intraepithelial lesion, adding the establishment of a histopathology diagnosis of anal pathology. The limitations of the study are the small sample size, that can, in itself, represent a bias for the determination of prevalences and statistical significances, so the results have a limitation to extend to the general population. Also, it was not possible to make a multivariate analysis, precisely due to the small sample size.

CONCLUSIONS

The present study highlights the importance of establishing protocols in Colombia to detect anal intraepithelial neoplasia in high-risk groups, such as patients with cervical intraepithelial neoplasia, or cervical cancer, and to encourage training in the use of high-resolution anoscopy, for specializations related with the diagnosis of anogenital pathology in Colombia, and globally, so that the detection of precursor lesions, and of

anal intraepithelial neoplasia be timely, and the treatment curtails its complications

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