

Intraepithelial Lesions and Uterine Cervical Neoplasms in Women in Juiz de Fora/Minas Gerais: Case-control Study

Lesões Intraepiteliais e Neoplasia Cervical Uterina de Mulheres Em Juiz de Fora/minas Gerais: Estudo Caso-controle

Lesiones Intraepiteliales y Neoplasia del Cérvico Uterino en Mujeres de Juiz de Fora/Minas Gerais: Estudio de Casos y Controles

RESUMO

Objetivo: determinar fatores relacionados à ocorrência de lesões citológicas precursoras em mulheres de Juiz de Fora/Minas Gerais assistidas na atenção básica. **Método:** estudo caso-controle entre 2017 a 2021. A amostra consistiu de 222 casos e 231 controles. Análises em três dimensões: sociodemográfica, sexual/reprodutiva e atenção à saúde. Odds ratios e intervalos de 95% de confiança calculados por regressão logística. **Resultado:** lesões precursoras reduzem com idade ≥ 60 anos, casadas, anticoncepcional injetável, coitarca > 15 anos, primeiro filho > 18 anos, 1 a 3 filhos e assistidas pela Estratégia da Saúde da Família. Fatores protetores para lesões precursoras: mulheres entre 30 a 39 anos, não utilizar preservativos, ensino médio, ≥ 4 gestações, ≥ 4 partos, citologia de repetição e assistidas pelo modelo tradicional. **Conclusão:** conhecer o perfil de mulheres susceptíveis ao desenvolvimento de lesões precursoras e neoplasia cervical uterina possibilita aos gestores e profissionais elaborar estratégias efetivas no rastreamento, detecção e diagnóstico. **DESCRITORES:** Programas de rastreamento; Neoplasias do colo do útero; Lesões intraepiteliais escamosas cervicais; Estudos de casos e controles.

ABSTRACT

Objective: To determine factors related to the occurrence of precursor cytological lesions in women from Juiz de Fora/Minas Gerais assisted in primary healthcare. **Method:** A case-control study conducted between 2017 and 2021. The sample consisted of 222 cases and 231 controls. Analyses were conducted in three dimensions: sociodemographic, sexual/reproductive, and healthcare attention. Odds ratios and 95% confidence intervals were calculated using logistic regression. **Result:** Precursor lesions decreased with age ≥ 60 years, being married, using injectable contraceptives, age at first intercourse > 15 years, first child > 18 years, having 1 to 3 children, and being assisted by the Family Health Strategy. Protective factors for precursor lesions: women aged 30 to 39 years, not using condoms, having completed high school, ≥ 4 pregnancies, ≥ 4 deliveries, repeat cytology, and being assisted by the traditional healthcare model. **Conclusion:** Understanding the profile of women susceptible to developing precursor lesions and cervical uterine neoplasia enables healthcare managers and professionals to develop effective strategies for screening, detection, and diagnosis. **KEYWORDS:** Screening programs; Cervical neoplasms; Cervical squamous intraepithelial lesions; Case-control studies.

RESUMEN

Objetivo: Determinar los factores relacionados con la ocurrencia de lesiones citológicas precursoras en mujeres de Juiz de Fora/Minas Gerais atendidas en la atención primaria. **Método:** Estudio de caso-control realizado entre 2017 y 2021. La muestra consistió en 222 casos y 231 controles. Se realizaron análisis en tres dimensiones: sociodemográfica, sexual/reproductiva y atención a la salud. Se calcularon los odds ratios y los intervalos de confianza del 95% mediante regresión logística. **Resultado:** Las lesiones precursoras disminuyen con edad ≥ 60 años, casadas, uso de anticonceptivo inyectable, coitarca > 15 años, primer hijo > 18 años, de 1 a 3 hijos y atendidas por la Estrategia de Salud de la Familia. Factores protectores para las lesiones precursoras: mujeres entre 30 y 39 años, no uso de preservativos, educación secundaria, ≥ 4 embarazos, ≥ 4 partos, citología repetida y atendidas por el modelo tradicional. **Conclusión:** Conocer el perfil de las mujeres susceptibles al desarrollo de lesiones precursoras y neoplasia cervical uterina permite a los gestores y profesionales elaborar estrategias efectivas en el rastreo, detección y diagnóstico. **DESCRIPTORES:** Programas de rastreo; Neoplasias del cuello uterino; Lesiones intraepiteliales escamosas cervicales; Estudios de casos y controles.

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INTRODUCTION

In Brazil, 704,000 incident cases of neoplasia are estimated for each year in the three-year period between 2023 and 2025, with 70% of these cases concentrated in the South and Southeast regions. For Cervical Cancer (CC), 17,010 new cases are expected in 2024, with an adjusted incidence of 13.25/100,000 women. This cancer is in third place for primary location and fourth for mortality in the female population, disregarding non-melanoma skin tumors.¹ In contrast to other regions of the country, there is a concentration of CC cases in the North and Northeast regions.^{1,2}

To achieve success in CC prevention and control actions, it is necessary to achieve high coverage and adequate frequency of cytology tests for women targeted by the screening program between the ages of 25 and 64.³ When suspicious changes are detected, they need to be diagnosed, monitored and treated appropriately.^{4,5}

The main strategy adopted in developed or developing countries to detect these changes and lesions in the epithelia is the cytopathological examination.^{6,7,9} It has become a relevant screening method for early detection of CC, due to its accuracy, easy execution and low cost.^{8,9} The cytopathological examination is quite efficient and used in the detection of atypia and cellular lesions that precede CC, in the initial stages, when treatment and follow-up measures allow high cure rates and, consequently,

reduced mortality.^{3,8,9}

The objective of this study is to determine factors related to the occurrence of precursor cytological lesions in women from Juiz de Fora/Minas Gerais assisted in primary care between 2017 and 2021.

METHOD

This is a case-control study¹⁰ to investigate the factors associated with precursor cytological alterations and/or CC. Data collection was performed using medical records from Basic Health Units (UBS) and the Gynecology outpatient clinic of a Specialized State Care Center (CEAE) in Juiz de Fora/Minas Gerais.

CEAE/Juiz de Fora is an outpatient service located at the headquarters of ACISPES (Pé da Serra Intermunicipal Health Cooperation Agency), and is a model of an intermunicipal health consortium in the Zona da Mata Mineira region. The institution offers consultations and exams of medium complexity in several specialties. CEAE is a micro-regional care point of the Minas Gerais State Health Department, with a specific target audience focused on offering specialized outpatient care services of regional reference for CC screening in 26 municipalities in Minas Gerais, including Juiz de Fora, ensuring comprehensive assistance to women, including educational, preventive, diagnostic and therapeutic actions.¹¹

To start treatment at CEAE, it is necessary to meet the criteria of the

state screening program with referrals made by the UBS. All selected women underwent colposcopy and/or cervical biopsy to confirm or rule out precursor lesions or CC between 2017 and 2021 at CEAE.¹¹

Sampling and study population

The sample was calculated using the methodology described by Woodward (2014)¹² considering the prevalence of precursor lesions of Human Papillomavirus (HPV) infection of 12.61% in Juiz de Fora (2015)¹³, 95% confidence level, study power 80%, relative risk estimate (Odds ratio – OR) of 1.0 and the ratio of one case to control, consisting of 222 cases and 231 controls.

Definition of cases and controls

Cases were defined as women aged 25 to 64 years with high-grade cytological lesions confirmed by histopathological study, treated at the Gynecology outpatient clinic. As for controls, women who underwent cytopathology tests in the selected period in 44 UBS without alterations in the cytology results were considered.

Cases were selected based on records found in biopsy records after colposcopies with alterations suggestive of precursor lesions and/or CC. Women defined as controls were selected from cytopathology test records and medical records at the UBS.

Controls were matched to cases according to age, UBS and year of cytopathological examinations. The pairing was performed by the expect-

ed frequency of control entry considering five age groups (<30, 30-39, 40-49, 50-59, ≥60 years) combined with the UBS of origin of the cases and the five-year period (2017, 2018, 2019, 2020, 2021).

The research trajectory was as follows: data collection began on women with high-grade cytological lesions/CC – cases – in the electronic medical records of the Gynecology outpatient clinic of CEAE/ACISPES from November 2021 to March 2022, and after this stage, information was collected from the medical records of women without cytological alterations – controls – between March 2022 and July 2022, in the UBS where the cases originated. Data were obtained from all seven administrative regions and 12 health regions of the municipality of Juiz de Fora.¹⁴

Inclusion and exclusion criteria

The inclusion criteria adopted were women aged between 25 and 64 years old^{1,3} and registered at the PHC of Juiz de Fora.

Data analysis

Based on the literature^{3,6,8,15}, selected the variables considered cofactors of risk for CC. To assess the sociodemographic dimension, the following variables were tested: age (<30, 30 to 39, 40 to 49, 50 to 59, ≥60), marital status (married, not married), race/color (white, non-white), and education (elementary or lower, secondary or higher).

For the sexual/reproductive dimension, the following variables were considered: menarche (≤11 years, >11 years), coitarche (≤15 years, >15 years), age at first birth (≤18 years, >18 years), number of children (0, 1-3, ≥4), use of barrier method - male condom (yes, no), use of contraceptive (yes, no). Regarding the variables related to screening (Health Care), three variables were selected: year the cytology was performed (2017, 2018,

2019, 2020, 2021), reason for the cytology (screening, repetition, follow-up) and whether the cytology was performed in the last 3 years (yes, no).

Data consolidation occurred in the Redcap (Research Electronic Data Capture)[®] program simultaneously with data collection. In the R software, version 4.3.0, bivariate analyses were performed between the factors associated with the outcome to estimate OR and respective 95% confidence intervals (95% CI). The variables that presented a p-value ≤ 0.2016 were included in the multivariate analysis model. The strategy adopted at this stage was to introduce the variables in the hierarchical modeling process according to the distribution of the variables in the three dimensions of analysis. To estimate the unadjusted and adjusted OR and their respective 95% CI, the reference category was defined as the one with the lowest risk for CC in the sample studied.

Ethical Aspects

The study was approved by the Research Ethics Committee on 12/19/2022 (CAAE 51800621.3.0000.5240) and met all ethical recommendations.¹⁷

RESULTS

A total of 453 women participated in the study. The mean age of cases was 40.57 years, standard deviation of 9.34 and p < 0.0001, and the mean age of controls was 46.87 years, standard deviation of 10.22 and p < 0.0001. There was a difference between the means of cases and controls of approximately 6.3 years. There was a greater chance of women having precursor lesions and/or CC in the age group between 30 and 39 (OR: 1.21 CI: 0.46-3.05) compared to women aged 60 years or older (OR: 0.21 CI: 0.06-0.66) who had 79% protection after adjustments for the selected variables.

Regarding marital status, married

women had lower chances of precursor lesions and CC than unmarried women (OR: 0.39 CI: 0.26-0.58). For race/color there was no statistically significant difference. For level of education, the chances of precursor lesions were higher in women who had a higher level of education, for those who had completed high school (OR: 1.55 CI: 1.02-2.36).

Regarding the sexual and reproductive dimension variables, for the use of barrier methods (male condoms), there was a slight chance of precursor lesions for women who used them (OR: 1.17 CI: 0.72 - 1.90). In both groups, both cases (83.5%) and controls (81.2%) did not use the barrier method during sexual intercourse, justified by the marital status since the majority were married women.

When observing the obstetric profile of the participants, women with a number of pregnancies ≥ 4 (OR: 1.2 CI: 0.77-1.88) and the number of births ≥ 4 (OR: 1.2 CI: 0.72 - 1.99) respectively, presented greater chances of precursor lesions. Regarding parity, for the age of first birth (OR: 0.49 CI: 0.31 - 0.49), women who had their first child > 18 years old had a lower chance of precursor lesions. Similar data were found for those who had coitarche over 15 years old (OR: 0.59 CI: 0.38 - 0.94). Regarding the number of children, the chance of having precursor lesions was lower for women who had between 1 and 3 children (OR: 0.51 CI: 0.27 - 0.94), compared to those who had ≥ 4 (OR: 0.73 CI: 0.34 - 1.58).

For the primary care modality, the vast majority of women were attended by the Family Health Strategy (FHS), with a slight chance of precursor lesions for women attended in the traditional UBS model (OR: 1.06 CI: 0.51 - 2.22). Table 01 presents the distribution of categorical variables regarding precursor lesions/CC in the study.

Table 01: Distribution of sociodemographic and sexual/reproductive characteristics among women with and without precursor lesions of CC.

Variables	Cases*	Control*	OR	CI 95%
	n (%)	n (%)		
Age				
<30	17 (7,7)	10 (4,3)	1	
30-39	101 (45,7)	49 (21,2)	1,21	0,46-3,05
40-49	59 (26,7)	73 (31,6)	0,48	0,18-1,2
50-59	33 (14,9)	68 (29,4)	0,29	0,11-0,75
>=60	11 (5)	31 (13,4)	0,21	0,06-0,66
Marital status				
Not married	101 (48,6)	60 (26,9)	1	
Married	107 (51,4)	163 (73,1)	0,39	0,26-0,58
Race/Color				
White	102 (45,9)	95 (41,3)	1	
Not White	120 (54,1)	135 (58,7)	0,83	0,57-1,2
Education				
Elementary or higher	95 (57,6)	143 (67,8)	1	
High school or higher	70 (42,4)	68 (32,2)	1,55	1,02-2,36
Do you use contraception?				
No	101 (48,6)	60 (26,9)	1	
Yes	96 (43,2)	78 (33,8)	0,67	0,46-0,98
Do you use a barrier method?				
No	182 (83,5)	186 (81,2)	1	
Yes, male condom	36 (16,5)	43 (18,8)	1,17	0,72-1,9
Number of pregnancies				
0-3	165 (75,3)	173 (78,6)	1	
≥4	54 (24,7)	47 (21,4)	1,2	0,77-1,88
Number of deliveries				
0-3	182 (82,4)	185 (84,9)	1	
≥4	39 (17,6)	33 (15,1)	1,2	0,72-1,99
Age at first birth (years)				
≤18	71 (42,8)	41 (27)	1	
>18	95 (57,2)	111 (73)	0,49	0,31-0,79
Menarche (years)				
≤11	45 (22,1)	41 (22,8)	1	
>11	159 (77,9)	139 (77,2)	1,04	0,64-1,69
Coitarcia (years)				
≤15	70 (34,3)	41 (23,7)	1	
>15	134 (65,7)	132 (76,3)	0,59	0,38-0,94
Number of children				
0	35 (16,6)	21 (9,7)	1	
1-3	137 (64,9)	163 (75,5)	0,51	0,27-0,94
≥4	39 (18,5)	32 (14,8)	0,73	0,34-1,58

Original Article

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UBS Modality				
FHS	200 (93)	212 (93,4)	1	
Traditional	15 (7)	15 (6,6)	1,06	0,51-2,22
Age – mean (SD)	40,57 (9,34)	46,87 (10,22)	0,0001	

*Totals may vary depending on unanswered variables (missing).

Source: the authors.

Regarding the cytological profile, women who underwent cytology in 2017 had lower chances of cytological lesions (OR: 0.74 CI: 0.51 – 1.07) compared to those who underwent it in 2020 (OR: 2.36 CI: 1.54 – 3.59).

Regarding the reasons for performing cytology, the chance of precursor lesions was higher for those who underwent it for repeat reasons, compared to those who underwent the exam for screening (OR: 54.7 CI: 25.84 – 124.01).

In the reasons that led women to undergo cytological collection, sta-

tistically significant differences were found in the OR, suggesting that the groups differ according to the reasons for performing the last cytology. For cytology tests performed in the last three years (2019, 2020 and 2021), the chance of precursor lesions was lower for these women (OR: 0.51 CI: 0.32 – 0.83), as shown in Table 02.

Table 02: Cytological profile of women aged 25 to 64 years, in Juiz de Fora, from 2017 to 2021.

	Cases*		Control*		OR	IC 95%
	N	%	N	%		
When have you done cytology?						
2017	96	43,2	117	50,6	0,74	0,51-1,07
2018	122	55	125	54,1	1,03	0,71-1,05
2019	128	57,7	125	54,1	1,15	0,8-1,67
2020	82	36,9	46	19,9	2,36	1,54-3,59
2021	96	43,2	83	35,9	1,36	0,93-1,98
Cytology reason						
Tracking	14	12,8	209	90,9	1	
Repetition	79	72,5	21	9,1	54,7	25,84-124,01
Follow-up	16	14,7	0	0	1	
Have had cytology in the last 3 years	169	76,1	199	86,1	0,51	0,32-0,83

*Totals may vary depending on missing variables.

Source: authors.

DISCUSSION

CC is a preventable public health problem when detected early. The lack of knowledge about the disease and its risk factors, the low awareness among women regarding primary and secondary prevention actions, and the need to develop effective public strategies aimed at this cancer with the aim of organizing screening and follow-up in primary and secondary care are still challenges to be over-

come.¹⁸

Screening programs are still inefficient in terms of early detection, occurrence of precursor lesions and cancer in early stages, and timely initiation of treatment, largely due to restricted access to health services and the predominantly opportunistic format of CC screening in Brazil. Despite advances in screening, control and prevention, high incidence and mortality rates for this neoplasm have remained.¹⁸

In a narrative review, factors that contribute to the occurrence of CC were presented, attributed to the per-

sistence of HPV infections, especially HPV 16 and HPV 18, representing almost 50% and 10% of cases, respectively. They also described factors related to HPV infection, such as early sexual debut, multiple sexual partnerships and early age at first child, and factors unrelated to HPV, such as low socioeconomic conditions and use of oral contraceptives.¹⁸

Findings of an integrative review¹⁹, highlighted the largest proportion of women affected by CC in the age group between 25 and 39 years, corroborating the results found here, where the greatest chances of precu-

sor lesions/CC were in women between 30 and 39 years old when compared to those aged 60 years or older. These data are in line with those observed in the literature, as there is a greater susceptibility to exposure and acquisition of high-risk HPV in women during adolescence if there is unprotected sexual intercourse. There is a greater possibility of developing persistent HPV infection with high-grade cytological lesions and CC in young women.¹⁹

Data on marital status indicated that married women had a lower chance of developing precursor lesions/CC than unmarried women. It is understood that women in long-term marital relationships and with regular sexual partners are less exposed to acquiring HPV, reducing the chances of persistent infection by this virus. In contrast to this situation, having multiple sexual partners is one of the risk factors for CC due to the greater risk of women being exposed to HPV infection when there is unprotected sexual intercourse.^{6,18} In the cross-sectional study carried out in Vitória (Espírito Santo), HPV infection was associated with multiple sexual partners (OR= 5.50 p= 0.028).¹⁵

In the present study, a slight chance of precursor lesions for CC was found in women who used condoms. However, in both analysis groups, women did not use this barrier method, with 83.5% and 81.2%, respectively cases and controls. These data serve as a warning because these women did not use male condoms in their sexual relations, and thus, can be considered vulnerable to acquiring HPV, despite being married.¹⁸⁻²⁰

Regarding the level of education, the chances of precursor lesions were higher for women with a higher level of education, mostly for those who had completed high school. It is worth noting that the number of years of study in relation to complete

high school was 12 years. In the analytical cross-sectional study carried out in Paraná, the majority of participants had completed high school (26.67%) and incomplete high school (23.33%), although the data did not relate schooling to the incidence of alterations in cytopathological exams.²¹

Regarding the variables of the sexual and reproductive dimension, the findings show that women who used contraceptives had a lower risk of precursor lesions, with a predominance of quarterly injectable contraceptives (progesterone-based) offered by the public health network. The use of contraceptives is considered a protective factor when the majority of study participants are married women, and thus, maintain steady sexual partners aiming at contraception.²¹

In a cohort study conducted in Denmark with women of reproductive age between 1995 and 2014, to determine the risk of CC associated with the use of hormonal contraceptives, it was found that women who used hormonal contraceptives compared to those who did not use them had a relative risk (RR) of 1.19 (95% CI 1.10 – 1.29) of developing CC.²²

When differentiating contraceptives, it was observed that those who used contraceptives during the study or recently of any type had a relative risk of 1.30 (95% CI 1.20-1.42), combined contraceptives had a relative risk of 1.40 (95% CI 1.28-1.53) and women who used progesterone-based hormonal contraceptives had a lower relative risk of 0.91 (95% CI 0.78-1.07). The study showed that the risk pattern among any user of isolated or combined contraceptives increased with the longer time of use and decreased after the interruption of this contraceptive method.²²

Observing the obstetric profile of the participants, women who had a number of pregnancies ≥ 4 and a number of births ≥ 4 respectively,

had a higher chance of precursor lesions. In a case-control study carried out in Pakistan (2024) to investigate the association between sociodemographic and behavioral factors, HPV infection and the progression of CC, it was found that women with higher parity had an additional factor for the occurrence of CC²³ corroborating the results found.

In the present study, regarding the number of children, the chance of having precursor lesions was lower for women who had between 1 and 3 children, compared to those who had ≥ 4 . Regarding parity, specifically for women who had their first child over the age of 18, these had a lower chance of precursor lesions. Similar data were found for women who had their first sexual intercourse (coitarche) over the age of 15. The age at the first child over 18 years and the age at coitarche over 15 years are relevant data in relation to the prevention of HPV infection and progression and precursor lesions for CC in young women, as they suggest that women had sexual intercourse later.

According to an integrative review²⁴, early sexual intercourse is directly related to an increased risk of cervical neoplasia due to several factors, such as the immaturity of the cervix in adolescence, intense metaplasia, the transformation zone of the cervix located in the ectocervix, and destabilized hormone levels.²⁴

Young women are more susceptible to changes caused by HPV infection, which regress spontaneously in most cases, but in a minority of women without effective preventive measures, they can contribute to cytological changes that evolve into CC. Physiologically, young adolescents are not always able to have sex, as they are undergoing a process of biological and hormonal changes, where their uterus can become more fragile, easily acquire infections and develop significant cytological changes over time.

“ Biological activity in adolescence is at its maximum level due to the body's adaptation to adult life, so the recommendation for women in adolescence would be to have sexual relations only when the body is mature, with preventive measures adopted, such as the use of barrier methods. ²⁴ ”

Regarding the type of care provided in primary care, most women were treated at UBS with the Family Health Strategy (FHS) and a minority were treated in the so-called traditional care model, which still exists in the municipality. There was a slight chance of precursor lesions occurring

in women treated in the traditional model. The FHS is a primary care model where strategies are developed for health promotion, disease and injury prevention, and group monitoring aimed at screening, detection, and early diagnosis of diseases, among which is cervical neoplasia, enabling more effective strategies such as active search and screening of women for this cancer.²⁵

Regarding the cytological profile, women who underwent cytology in 2017 had a lower chance of cytological lesions compared to those who underwent cytology in 2020. When observing the reasons for performing cytology, the chance of having precursor lesions was much higher for those who were referred for repeat cytology compared to those who underwent the exam for screening, justifying that repeat cytology tests are preceded by some cytological alteration. These alterations need to be monitored and monitored effectively to assess the conditions of evolution or regression, and thus, professionals, faced with the dynamics of the follow-up, must adopt flowcharts, guidelines and care and preventive procedures aimed at the survival and resolution of the detected and monitored alterations.^{3,6,8}

Considering the reasons that led women to undergo cytopathological collection, statistically significant differences were found in the OR, suggesting that the groups differ according to the reasons for performing the last cytology. Regarding the performance of cytology in the last three years (2019, 2020 and 2021), the chance of precursor lesions was lower for these women. According to the Brazilian guidelines and recommendations to be adopted regarding the frequency of cytological collection in the screening of cervical neoplasia, it is observed that women who underwent two consecutive annual exams with negative results can perform a new cytological collection in three

years, ensuring satisfactory levels of prevention, which corroborates the findings in this study.^{3,6,8}

CONCLUSION

The factors that contributed to the greater chances of developing precursor lesions and/or CC are: age range between 30 and 39 years, non-use of barrier methods (male condoms) during sexual intercourse, complete high school, women who had ≥ 4 pregnancies and \geq births, having undergone cytological collection in the last three years, needing repeat cytology and being assisted by primary care using the traditional care model. When considering the protective effect of the factors that reduced the chances of lesions, women aged ≥ 60 years, being married, using injectable contraceptives quarterly, with 1 to 3 children, coitarche over 15 years old, having had their first child over 18 years old and having been assisted by the FHS are listed.

By determining the characteristics, behaviors and care measures relating to the tracking, control and follow-up measures of CC, knowledge is provided so that managers and health professionals can act effectively on the profile of women considered more susceptible to the development of precursor lesions and cervical uterine neoplasia.

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