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Natural History of Precancerous Cervical Lesions: an Exploratory Study of a Cohort of Women from Rio de Janeiro - RJ, Brazil

História Natural de Lesões Precursoras do Câncer do Colo do Útero: Estudo Exploratório de uma Coorte de Mulheres do Rio de Janeiro - RJ, Brasil

Historia Natural de las Lesiones Precursoras del Cáncer del Cuello del Útero: un Estudio Exploratorio de una Cohorte de Mujeres de Río de Janeiro - RJ, Brasil

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Abstract

Introduction: Cervical Intraepithelial Neoplasia (CIN), when untreated, is likely to progress to cancer, persists as CIN, or regresses to a normal tissue. **Objective:** To determine the pattern of natural evolution of precancerous lesions of the cervix, and to evaluate the role of co-factors on the risk of cervical cancer development in a cohort of women from Rio de Janeiro, Brazil. **Method:** An exploratory study was carried out in 227 women with precancerous lesions referred from the Cervical Pathology Center from 1998 to 2000. The evolution of precancerous lesions was ascertained in patients who were left untreated for presenting clinical limitations. Patients were followed for two years, with a cytological exam. Cytological results were classified as follows: Low grade Squamous Intraepithelial Lesion (LSIL), high grade Squamous Intraepithelial Lesion (HSIL). Likelihood and risk of regression, persistence and progression of precancerous lesions were determined using the Kaplan Meier test (L-R:95%) and the Proportional Cox Regression test. **Results:** The lesion regression likelihood was the following: 46% (LSIL), 72.8% (HSIL). HSIL was more likely to persist (43.1%) and progress to cervical cancer (7.1%) than LSIL. Women <30 years were more likely to regress (79.9%) than older women, and women ≥50 were more likely to show lesion persistence (43.3%) and to progress to cervical cancer (31.8%) than younger women. **Conclusion:** Women <30 years at diagnosis of LSIL were more likely to regress than older women, and women ≥50 years with HSIL were at higher risk persistence and progression, when compared to younger women.

Key words: Uterine Cervical Neoplasms/epidemiology; Precancerous Conditions; Cervical Intraepithelial Neoplasia; Natural History of Diseases

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INTRODUCTION

Cervical cancer still remains a public health problem in Brazil, as it is the second major cause of death from cancer, among women in this country[1].Although cervical cancer risk has substantially declined among women in developed countries, due to effective cervical cytology screening programs, this neoplasia continues to be the most common cause of premature death among middle-aged women and the largest single cause of cancer related deaths in developing countries[2-4].

While HPV is the most common sexually transmitted infection, cervical cancer is a rare consequence of a high-risk HPV (HR-HPV) infection[5]. This fact suggests an important environmental role (i.e. Oral contraceptive use, sexual onset at an early age, early menarche, tobacco smoking, co-infection of Sexual Transmitted Disease, and so on) and genetics cofactors, interacting with the carcinogenic transformation of HPV infected cervical epithelium[6-7].

After a HR-HPV infection, Low grande Intraepithelial Neoplasia (LSIL) can arise. A high proportion of LSIL usually regresses spontaneously if left untreated, but if HR-HPV infection persists, LSIL may progress to HSIL. Because these lesions are recognized as precancerous lesions, it is generally recommended to treat them through surgical ablation. Otherwise, HSIL may persist or progress towards invasive carcinoma[8].

Therefore, it is a common practice in Brazil to refer all women with a HSIL smear for immediate colposcopical and histological evaluation, and further for ablation surgery for those with histologically confirmed HSIL. The recommendation for LSIL is to repeat the cytological examination and if repeated cytological lesion is present, colposcopy is indicated and further lesion excision[9].

Short-term follow-up studies comparing different screening strategies for women with LSIL have shown differences in the proportion of spontaneous regression for different ages, with 50-80% in adults[10-11] and more than 90% in college students from age 18 to the early 20s[12].

Since following subjects with precancerous lesions is ethically unacceptable, few studies on the natural history of cervical cancer have been developed. An alternative approach is to carry out studies based on the registry of medical records to passively follow such subjects. Thus, there are some clinical conditions that might keep women from being submitted to cervical ablation procedures in the cervix, such as pregnancy, cervical infection, and unsatisfactory colposcopy. In a Health Center specializing in cervical pathologies in the city of Rio de Janeiro, Brazil, a group of women with an abnormal Pap exam had no clinical conditions to be submitted to a surgical procedure in the cervix. This fact enabled us to study the natural history of the precancerous lesion of the cervix. This study was carried out in an effort to determine the pattern of natural evolution of precancerous lesions of the cervix and to evaluate the role of co-factors on the risk of cervical cancer development in a cohort of women from Rio de Janeiro, Brazil.

METHOD

Study population

An exploratory study was carried out in a cohort of women with cytological diagnosis of HSIL or two consecutive LSIL, referred to a Cervical Pathology Health Center in the State of Rio de Janeiro in Bangu (PAM Bangu) for a colposcopy exam, from January 1998 to December 2000.

From the 821 women referred to the Health Center, 491 were treated by surgical procedures[13] and 330 (37.9%) remained temporarily untreated by LEEP (loop electrical excision procedure) due to the following conditions: no observed lesion at colposcopy exam (40.5%), cervical infection (18.1%), pregnancy (17.2%), unreported reasons (15.4%), and chronic conditions such as hypertension, cardiopathy, or diabetes (8.8%). From those 330 untreated patients, 227 (68.8%) had at least one follow-up Pap smear exam, allowing for the analysis of the natural history of precancerous lesions of the cervix. Thus, the study population is 227 Brazilian women from the city of Rio de Janeiro, with a cytological diagnosis of CIN, who were left untreated, and had at least one follow up Pap smear exam, from 1998 to 2000.

Clinical procedures

Two specialized gynecologists collected clinical and epidemiological information, along with the gynecological background, and carried out the colposcopic examination at the first patient attendance in the Health Center. Patients, who were pregnant at the time of the colposcopy, were followed until delivery and then, if they still had an altered pap exam, were treated after giving birth. The analysis stratifying the cohort according to pregnancy status was carried out, and this variable did not modify the lesion progression results observed in the whole studied sample (data not shown).Women presenting hypertension, heart disease, or atrophic cervix, were left untreated and followed until they underwent a cold knife conization at the surgical center in the hospital. All those who had cervical inflammation were followed-up by a pap test and treated with specific medication before undergoing the excision of the lesion. According to the Brazilian National Protocol for Women's Health, women left untreated after an altered Pap exam should be followed every 3 months until the excision of the lesion is clinically possible to be performed.

Smears for a conventional pap test were collected with an Ayre spatula (for ectocervix sample) and a brush (for endocervix sample), and placed over a slide, which was immersed in alcohol at 96%. All the slides were analyzed by pathologists from the Integrated Cytopathology Technology Section (SITEC) of the Brazilian National Cancer Institute, which diagnoses less than 5% of undetermined squamous cell carcinoma and/or undetermined adenosquamous cell carcinoma (ASCUS/AGUS)[14]. This service has a coverage reaching 95% of all the cytological and histological examinations carried out in the city of Rio de Janeiro.

The Cervical Pathology Health Center in Bangu is a public health center settled in a low income area, being the only local public reference for cervical pathology diseases.

Data collection and variable classification

Study data was taken from a data base of the project "Cervical cancer control", developed by the National School of Public Health in Brazil and the Municipal Health Secretary of Rio de Janeiro. Social and demographic profile, clinical and gynecological background, smoking antecedents, colposcopic findings, and cytological results were collected from medical records, following a standardized form.

Current cytological information was cross-tabulated with the reports recorded at the cytological reference center (SITEC), which classified them according to the Bethesda System classification[15] as LSIL and HSIL (for cytological reports). Clinical and epidemiological records were obtained as follows: age (years), education (up to 8 years and 8years or more), age at first sexual intercourse (years), number of sexual partners, parity and menopause status (yes/no). In relation to smoking antecedents, women were classified as smokers (current or former smokers) or non-smokers; as well as specifying duration of tobacco smoking in years. Oral contraceptive use was classified as users or non-users, and duration of use in months. Age at first sexual intercourse, number of sexual partners and duration of smoking habit were analyzed using specific cut-off points based on boththe used cut-off in the same population[13], and the studied sample distribution parameters (mean and median).Tobacco exposure data was retrieved from medical records, and stratified as ever smokers or non-smokers.

Statistical analysis

Descriptive analysis was carried out to evaluate the distribution of the variables and their correlation with the lesion degree. The relationships among discrete variables were assessed by pairwise comparisons using two-side chi-square test, and a statistical significance of 5%was used.

Survival analysis was performed in 2 years of follow-up after the first colposcopic exam, aiming to evaluate the dynamics of natural evolution of each pre-cancer lesion using the pairwise Kaplan-Meier method, making comparisons between the age groups and the severity of the lesions at the entrance to the study (Log-Rank test: 95%). In this step, a survival analysis was carried out to estimate the conditional probability of lesion progression, persistence, and regression. Additionally, the effect of selected risk factors related to the persistence and progression of precancerous lesion was carried out. Two normal cytological results (disease-free) following the altered entrance cytology were classified as lesion regression. Another cytological result with the same lesion degree following the altered entrance cytology was classified as lesion persistence. A HSIL or cancer on the cytological result following the altered entrance cytology was considered lesion progression, for LSIL. LSIL or HSIL diagnosis subsequent to a former LSIL or HSIL respectively altered cytology were considered as lesion persistence, being the follow-up time length based on the second smear. Regarding persistence and progression, women who did not present any altered Pap test at the end of 24 months were censored, and those who did not complete 24 months of follow up were censored in the date of the last Pap test. Also, women who presented a higher grade lesion following the altered entrance cytology were censored for persistence and regression. On the other hand, women who presented the same lesion grade following the altered entrance cytology were censored for progression and regression.

A multiple proportional Cox regression model was constructed to evaluate factors predicting the regression to the normal cytological result, by estimating crude and adjusted Hazard Ration (HR and adjHR, respectively). Independent variables shown to be statistically significant in uni-variate analysis were entered in the binary proportional Cox regression model through the *Enter* method, using the default values as criteria to enter ($p<10\%$) and remove ($p>5\%$). A probability value less than 0.05 was regarded as statistically significant. The final Cox Model was carried out by evaluating SIL persistence and progression according to selected explanatory variables and adjusted by age and education, both presenting biological meaning and statistical significance for the studied outcomes. A t-trend test was carried out asiming to explore the occurrence of possible trends with categorical variables risk estimates. Epi Info software (version 6.04d, 2001; Center for Disease Control and Prevention (CDC), Atlanta, Georgia, USA) and SPSS software (version 10.0) were used to carry out the analysis.

Ethical issues

The present study follows the 196/96 resolution of Brazilian National Research Council, and has a

retrospective design based on medical record files, being carried out using the Rio de Janeiro municipality health authority data base. Therefore, when this study started, all clinical procedures including the standard clinical routine, lesions treatment and patients' follow-up had already been performed; therefore the Ethics Committee of the Brazilian National School of Public Health, Ministry of Health, considered that an informed consent of each participant was not required. This investigation was approved by the Ethics Committee of the Brazilian National School of Public Health, with the following protocol number 52/02 on January 1st 2002.

RESULTS

Descriptive analysis shows that age, marriage *status*, educational level, number of pregnancies, number of birth deliveries and menopause *status* were statistically related to the grade of precancerous lesions(Table 1).The highest CIN-1 prevalence (60%) was observed among women up to 30 years old, while the highest CIN 2/3 prevalence was verified among women over 30 years old (~40%). Antecedents of 2 or more pregnancies were observed for 86.4% of women with CIN-3, and 60% of women with CIN-1. The majority of women were single regardless the lesion grade (55%, 55.2% and 39.5%, for CIN-1, CIN-2 and CIN-3, respectively).

Table 2 shows precancerous lesion evolution in 24 months. According to this table, 46% of CIN1 are likely to regress to negative cytological result, while for CIN2 and CIN3 such results were, respectively, 38.4% and 34.4% (LR:95%*p-value=0.2522*). On the other hand, CIN3 is statistically more likely to persist (43.1%) than CIN2 (26.3%) and CIN1 (25%) (LR:95% *p-value=0.0138*). Though CIN1 is more likely to progress to a higher grade lesion (17.5%), CIN2 and CIN3 have a probability of progression to cervical cancer of 6.1% and 7.1%, respectively (LR:95%*p-value=0.0920*). In relation to the likelihood of lesion persistence, older women (39-49 and ≥50 years old) were statistically more likely than younger women to show persistent lesions (42.3% and 43.3%, respectively, LR:95%*p-value=0.0018*). Women over 50 years were statistically more likely to progress to a higher degree lesion (31.8%) than women under this age (LR:95%*p-value=0.0182*).

Multi-variate analysis shows that women at older ages (≥ 50 years) are at higher risk of persistence of precancerous lesions (adjHR=6.53,CI:95%:2.4–18.1) or lesion progression (adjHR=9.19,CI95%:1.0-82.4), in 24 months of follow-up (Table 3). There was also a statistically significant trend between age categories for persistence and progression of precancerous lesions.

DISCUSSION

It is well known that cervical precancerous and cancerous lesions are consequences of causes that operate over years, often decades, and that the most important of them is HR-HPV infection[5]. However, the dynamics of the natural evolution of CIN is hard to ascertain, especially because most of HPV infections are transient and the exposure to co-factors may vary according to age groups, affecting the precancerous lesion risks of persistence and progression[8]. The infection is transmitted at early ages after the first sexual intercourse, being widespread among 25 to 30 year old women, and a second peak has been reported among women over 55 years of age[16].

Our results show that regression seemed not to differ according to the lesion grade (LR:95%=*0.2522*). Those findings might be explained by the fact that though CIN-1 cytology is now accepted to represent acute HPV infection, this may sometimes be associated with CIN-2/3 cytology. A study of the incidence of HPV infections in teenagers found that the risk of CIN-2/3 was greatest in the six months after the first detection of HPV, with a rapid decline thereafter[17].

However, Li et al.[18] documented that two-thirds of young women with high viral loads of HPV had no abnormal cytology, showing that cytological abnormalities are not a constant following to HPV infection. The median time to clear HPV infection varies with clearance definition (e.g., how many tests and over what time period were performed) and the estimates range from 8 to 18 months[19]. Thus, it has been found that cytological regression occurs five to six months before HPV clearance, which is plausible given the speed with which cervical epithelium regenerates[20].

Those findings are also supported by a large longitudinal study conducted in Brazil between 1993 and 2002[21]. A total of 2,404 women between 14 and 60 years were followed with cytology exam for two years, every four months in the first year and, thereafter, every six months. The authors found that LSIL is more likely to regress in six (51%) and 12 months (78%) than to progress in six (1.7%) and 12 months (3.6%).

Studies examining the natural history of HSIL disease, based on observations made in the 1950s and 1960s, have estimated an annual rate of progression to invasive cervical cancer of less than 1%[22]. In this sense, our study found that CIN-3 persistence was higher comparatively to that observed with CIN-1 and CIN-2 (LR:95%=*0.0138*), but no difference on the risk of progression was found. In interpreting this data, it is important to consider that those studies were conducted at a time when the age profile of women screened was older than today, being

Table 1. Epidemiological characteristics of Brazilian women with pre-cancer lesion

Variables	CIN-1 (n= 20)	CIN-2 (n=163)	CIN-3 (n=44)	*p-value*
	n (%)	n (%)	n (%)	(X^2)
Age (yrs)				
10 – 29	12 (60.0%)	82 (50.3%)	82 (50.3%)	0.000
30 – 49	07 (35.0%)	64 (39.3%)	64 (39.3%)	
≥ 50	01 (5.0%)	17 (10.4%)	17 (10.4%)	
Ethnic group				
White	6 (40.0%)	68 (51.9%)	68 (51.9%)	0.071
Black	3 (20.0%)	6 (4.6%)	6 (4.6%)	
Multiracial	6 (40.0%)	57 (43.5%)	57 (43.5%)	
Marriage *status*				
Single	11 (55.0%)	90 (55.2%)	90 (55.2%)	0.017
Married	09 (45.0%)	60 (36.8%)	60 (36.8%)	
Widow/divorced	0 (0%)	13 (8.0%)	13 (8.0%)	
Education				
≤ Middle school	6 (30.0%)	45 (27.6%)	45 (27.6%)	0.032
> Middle school	14 (70.0%)	118 (72.4%)	118 (72.4%)	
Menarche				
≤ 12 years	6 (31.6%)	67 (41.1%)	67 (41.1%)	0.590
> 12 years	13 (68.4%)	96 (58.9%)	96 (58.9%)	
1st Sexual intercourse				
≤ 18 years	9 (45.0%)	120 (73.6%)	120 (73.6%)	0.097
> 18 years	11 (55.0%)	43 (26.4%)	43 (26.4%)	
Pregnancies				
≤ 2	12 (60.0%)	84 (54.6%)	84 (54.6%)	0.000
>2	08 (40.0%)	74 (45.4%)	74 (45.4%)	
Birth deliveries				
< 2	11 (55.0%)	71 (43.6%)	71 (43.6%)	0.000
≥ 2	09 (45.0%)	92 (56.4%)	92 (56.4%)	
Menopause				
Yes	02 (10.0%)	21 (12.9%)	21 (12.9%)	0.000
No	18 (90.0%)	142 (87.1%)	142 (87.1%)	
Sexual partners				
≤ 2	15 (75.0%)	105 (64.8%)	105 (64.8%)	0.560
> 2	05 (25.0%)	57 (35.2%)	57 (35.2%)	
Contraceptive use				
Former/current	07 (35.0%)	74 (45.4%)	74 (45.4%)	0.218
Never	13 (65.0%)	89 (54.6%)	89 (54.6%)	
Duration of contraceptive use				
≤ 12 months	13 (68.4%)	105 (66.9%)	105 (66.9%)	0.134
> 12 months	06 (31.6%)	52 (33.1%)	52 (33.1%)	
Tobacco smoking				
Yes	08 (32.0%)	34 (21.4%)	34 (21.4%)	0.517
No	17 (68.0%)	125 (78.6%)	125 (78.6%)	
Duration of tobacco smoking				
< 20 years	06 (75.0%)	51 (86.4%)	51 (86.4%)	0.059
≥ 20 years	02 (25%)	08 (13.6%)	08 (13.6%)	

Table 2. Natural evolution of precancerous lesions of the cervix in 24 months of follow up. (Kaplan–Meier analysis)

Variable	Regression*	Persistence	Progression
Pre-cancer lesion			
CIN-1	46.0%	25.0%	17.5%**
CIN-2	38.4%	26.3%	6.1%***
CIN-3	34.4%	43.1%	7.1%***
Log-Rank p-value:95%	*0.2522*	*0.0138*	*0.0920*
Age group			
10 – 29 years	79.9%	10.4%	1.1%**
30 – 49 years	60.1%	42.3%	9.5%***
≥ 50 years	45.9%	43.3%	31.8%***
Log-Rank p-value:95%	*0.0795*	*0.0018*	*0.0182*

*Regression to normal Pap smear test; ** Progression to CIN-2 and CIN-3/cancer (for CIN-1 and CIN-2, respectively) Pap smear test; *** Progression to invasive cancer

Table 3. Crude and adjusted hazard ratio for persistence and progression of precancerous lesions of cervical cancer, among Brazilian women (proportional Cox regression analysis)

Variables	Persistence**		Progression**	
	Crude HR (CI:95%)	Adj. HR* (CI:95%)	Crude HR (CI:95%)	Adj. HR* (CI:95%)
Age (yrs)				
10 – 29	1	1	1	1
30 – 49	2.01 (0.9 – 2.2)	2.21 (0.9 – 5.7)	8.45 (1.04-68.7)	7.02 (0.9– 57.1)
≥ 50	4.50 (1.3 – 3.4)	†6.53 (2.4 – 18.1)	13.16(1.5–117.9)	†9.19 (1.0 –82.4)
Ethnicity (skin color)				
White	1	1	1	1
Black	1.12 (0.1 – 8.9)	1.42 (0.2 – 11.4)	6.15 (0.5 – 69.7)	7.68 (0.7 – 90.8)
Multiethnic	0.72 (0.3 – 1.7)	0.90 (0.4 – 2.2)	2.51 (0.5 – 12.9)	1.80 (0.3 – 9.5)
Menarche				
> 12 years	1	1	1	1
≤ 12 years	1.23 (0.6 – 2.7)	1.35 (0.6 – 2.9)	0.53 (0.1 – 2.0)	0.62 (0.2 – 2.3)
Age at 1st sexual onset				
> 18 years	1	1	1	1
≤ 18 years	1.85 (0.9 – 4.0)	1.47 (0.7 – 3.2)	2.02 (0.4 – 9.2)	2.46 (0.5 – 11.4)
Pregnancies				
≤ 2	1	1	1	1
> 2	1.95 (0.9 – 4.3)	1.31 (0.5 – 3.2)	4.95 (1.1 – 22.6)	2.58 (0.5 – 13.7)
Parity				
< 2	1	1	1	1
≥ 2	2.21 (0.9 – 5.2)	1.80 (0.7 – 4.5)	8.43 (1.1 – 65.3)	4.83 (0.6 – 42.3)
Menopause				
No	1	1	1	1
Yes	2.06 (0.9 – 4.9)	0.90 (0.2 – 3.1)	3.31 (1.1 – 10.5)	1.16 (0.2 – 7.2)
Number of sexual partners				
≤ 2	1	1	1	1
> 2	1.18 (0.5 – 2.6)	1.33 (0.6 – 2.9)	1.06 (0.3 – 3.5)	1.03 (0.3 – 3.4)
Contraceptive use				
Non-user	1	1	1	1
Current/former user	0.43 (0.2 – 1.0)	0.61 (0.3 – 1.5)	0.92 (0.3 – 2.9)	1.76 (0.5 – 6.6)
Tobacco smoking				
Non-smoker	1	1	1	1
Current/former smoker	1.21 (0.5 – 2.8)	1.33 (0.6 – 3.1)	1.83 (0.5 – 6.3)	1.70 (0.5 – 5.8)
Duration of tobacco smoking				
< 20 years	1	1	1	1
≥ 20 years	2.13 (0.6 - 8.1)	1.28 (0.3 – 4.9)	2.11 (0.5 – 8.5)	1.37 (0.3 – 6.8)

* Adj.HR (adjusted Hazard Ratio): Adjusted by age and education; ** Any kind of lesion (CIN-1, CIN-2/3)
† p-trend ≤ 0.05

poorly screened, and the quality of cytology was also poorer. All of these factors would lead to a rate of cancer, subsequently to a CIN-2/3 cytology result, higher than could be currently expected.

The present study shows that 25% of CIN-1 persisted likewise along a 24 month follow-up, being such figures of 26.3% for CIN-2 and 43.1% for CIN-3. Similar results were found by Ostör23 who summarized all written articles over the preceding 40 years that addressed the natural history of cervical neoplasia. The authors found that 43% of CIN-2 and 33% of CIN-3 regress, 26.3% persist as CIN-2 and 56% persist as CIN-3, 22% of CIN-2 progress to CIN-3, and 12% of CIN-3 progress to cancer, over an undetermined period.

Apart from persistent precancerous lesions, another factor known to influence the progression of precancerous lesion is age. The results of this study show that the probability of lesion persistence and progression are age-related (Table 2 and 3). According to these findings, the probabilities of persistence and progression are statistically different between age groups in such a way that women over 30 years are 42.3% more likely to have a persistent lesion compared to younger women (LR:95%=*0.0018*). Also, while only 1.1% of women from 10 to 29 years present with a cytology progression, 9.5% of women 30-49 years and 31.8% of women ≥ 50 years are statistically likely to present with a cytological progression to a higher grade lesion (LR:95%=*0.0182*).

This study also observed that women 50 years or older were at statistically higher risks of lesion persistence and progression than women between 10-29 years of age, respectively, adjHR=6.53 and adjHR=9.19. These findings are supported by An et al.[24] who observed that Korean women ≥ 45 years is more likely to persist as HSIL (29,4%)and those who were ≥ 51 years were more likely to progress to cancer (37,5%) than younger women.

Although the present study did not evaluate the extension of the lesions, the findings could be explained by the fact that, besides age, there is evidence that the extent of CIN-2/3 may influence the progression to cancer. Biopsy-proven microinvasive cancer is typically associated with extensive CIN-3, both on the surface epithelium and also affecting the deep endocervical crypts[22]. Sun et al.[25] developed a study in Taiwan, China, revealing that the effect of HPV infection on SIL development is highly influenced by high viral load and highlighted a potential application of viral load testing in predicting the size and severity of lesions of the uterine cervix.

Also, in the last years, several prospective studies evaluated the natural history of SIL (and in particular HSIL) in pregnant women showing a very low progression rate to invasive cancer, ranging from 0% to 9.7%[23,24]. Thus, though in the present study the progression rates of CIN2/3 to cancer were the same of those studies, a higher progression rate was found when we evaluated according to age groups, probably because we included women not only in the fertile age.

Finally, although ethnicity (black skin color), current tobacco smoking, duration of smoking (>20 years), age at sexual onset (<18 years old), parity and number of pregnancies were associated with the risk of progression, none of these were statistically significant.

A limitation of the present study was a small sample size, which yielded to wide confidence intervals, thus jeopardizing the possible inferences of the observed results. On the other hand, the analyzed sample was not an author's choice, but the available universe at the Cervical Pathology Health Center in the State of Rio de Janeiro in Bangu (PAM Bangu). This limitation may explain the absence of statistical significance for the observed association between environmental and behavioral risk factors and the persistence and progression of precancerous lesions.

Even though the cytological results were validated with the reports recorded at the cytological reference center (SITEC), environmental and behavioral information were under the limitations of a retrospective design, based on medical records. Thus, the interviewing of the participants may not have followed standardized criteria, leading to a possible misclassification of the explored exposures, and therefore underestimating the associations found. Another limitation of the present study, also related to a retrospective study based on medical records, is that we were not able to present the different subtypes of HR-HPV, possibly associated with a progression of such lesions.

Despite such limitations, this investigation has some strength. The topic of thenatural history of cervical precancerous lesions is poorly reported in literature, considering the ethical limitations to explore it. In this investigation, we found an acceptable way to carry out such evaluation, without harming the health of affected women by following those women for whom LEEP was not indicated. Moreover, the investigation was carried out in women from a developing country, whose population usually has high exposure to HPV transmission if their sexual behavior is considered (number of sexual partners, age of first sexual intercourse).

Therefore, even after considering the aforementioned limitations, the observed data seems to enhance the understanding of the dynamics of precancerous lesion evolution in the studied population.

CONCLUSION

In summary, age seems to present a demonstrable effect on the likelihood of CIN persistence and progression, in such a way that, comparatively to women 10 to 29 years,

those 30 to 49 years and those 50 years or older, are at higher risk of CIN persistence and progression. Similarly, women presenting CIN-3 are more likely to persist than women presenting a CIN-1 or CIN-2 lesion.

In this sense, this study provides evidence that when looking at a precancerous lesion, the clinical decision made for treating or watchful waiting must take into account the age of the woman and the degree of the precancerous lesion.

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CONTRIBUTIONS

IFS carried out the study concept, study design, definition of intellectual content, literature research, statistical analysis, and manuscript preparation. RJK participated in the conception, design, statistical analysis, and definition of intellectual content. SK participated in the manuscript edition/review. IEM carried out the manuscript edition/review, and participated in the study concept, study design, and definition of intellectual content.

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Resumo

Introdução: Neoplasia de Itraepitelial Cervical (NIC) quando não tratada progride para câncer, persiste como NIC ou regride para um tecido normal. **Objetivo:** Determinar o padrão de evolução natural das lesões precursoras do câncer cervical e avaliar o papel de cofatores sobre o risco de desenvolvimento dessa neoplasia numa coorte de mulheres do Rio de Janeiro, Brasil. **Método:** Foi feito um estudo exploratório em 227 mulheres com NIC referidas a partir do Centro de Patologia Cervical, de 1998 2000. A evolução das NIC foi verificada em pacientes que foram deixadas sem tratamento por apresentarem limitações clínicas, que foram seguidas por dois anos com exames citológicos. Resultados citológicos foram classificados como: Lesão de Baixo Grau (LBG), Lesão de Alto Grau (LAG). Probabilidade e risco de regressão, persistência e progressão das lesões pré-cancerosas foram determinados usando test (L-R:95%) de Kaplan Meier e regressão de Cox proporcional. **Resultados:** A probabilidade de regressão da lesão foi: 46% (LBG), 72,8% (LAG). As LAG apresentaram maior probabilidadde de progressão para câncer (7,1%) e persistência (43,1%) do que LBG. Mulheres <30 anos eram mais propensas a regredir (79,9%) do que as mulheres mais velhas. Mulheres ≥50 eram mais prováveis de apresentar lesão persistente (43,3%) do que as mulheres mais jovens (31,8%). **Conclusão:** Mulheres < 30 anos no diagnóstico de LBG eram mais propensas a regredir do que as mulheres mais velhas. Mulheres com ≥50 anos com HSIL eram mais sujeitas a ter lesões persistentes e progredirem, em comparação às mais jovens.

Palavras-chave: Neoplasias do Colo do Útero/epidemiologia; Lesões Pré-Cancerosas; Neoplasia Intra-Epitelial Cervical; História Natural das Doenças

Resumen

Introducción: Cuando la Neoplasia Intraepitelial Cervical (NIC) no es tratada puede evolucionar en cáncer, persistir como NIC o retroceder a tejido normal. **Objetivo:** Determinar el patrón de evolución natural de las lesiones precursoras del cáncer del cuello del útero y evaluar el papel de cofactores de riesgo del cáncer del cuello del útero en una cohorte de mujeres de Río de Janeiro, Brasil. **Método:** Se ha realizado un estudio en 227 mujeres con NIC referidas a partir del Centro de Patología Cervical (1998-2000). La evolución de las NIC fue verificada en pacientes que no han sido tratadas debido a limitaciones clínicas, que fueron seguidas por dos años con pruebas citológicas. Los resultados citológicos han sido clasificados como: lesiones de bajo grado (LBG) y lesiones de alto grado (LAG). Probalidad y riesgo de retrocesión, persistencia y progresión de las lesiones precancerosas han sido determinadas mediante prueba de Kaplan Meier (L-R: 95%) y regresión de Cox proporcional. **Resultados:** La probabilidad de regresión de la lesión fue 46% para LBG y 72.8% para LAG. Las LAG presentaron mayor probabilidad de progresión para el cáncer (7.1%) y persistencia (43.1%) que las LBG. Las mujeres <30 años presentaron mayor probabilidad de regresión (79.9%) que las mujeres más mayores, y mujeres ≥50 años eran más propensas de presentar lesión persistente (43.3%) que las mujeres más jóvenes (31.8%). **Conclusión:** Mujeres <30 años en el diagnóstico de LGB eran más propensas a retrocesión que mujeres más mayores, mientras que mujeres ≥50 años con HSIL estaban más sujetas a tener lesiones persistentes y progresión que la mujeres más jóvenes.

Palabras clave: Neoplasias del Cuello Uterino/epidemiología; Lesiones Precancerosas; Neoplasia Intraepitelial del Cuello Uterino; Historia Natural de las Enfermedades