Clinical and evolving features of women diagnosed with precancerous cervical lesions, screened and treated in the Amazon region of Brazil

Características clínicas e evolutivas de mulheres com diagnóstico de lesões precursoras de câncer cervical, rastreadas e tratadas na região amazônica brasileira

Las características clínicas y los resultados de mujeres con un diagnóstico de lesiones precursoras de lesión cervical, seguimiento y tratamiento en la Amazonia brasileña

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Abstract

The objective of the study was to determine the dynamics of precancerous lesions in women of a cohort treated for cervical intraepithelial neoplasia (CIN) and followed up over the next two years. The conditional probability of failure was calculated using the Kaplan-Meier method, and the raw and adjusted hazard ratios (HR) were determined using Cox regression with a p-value entry of < 0.05. Of the 237 women who were treated, 51.5% were accompanied over 24 months, and treatment failed for 21.9% of those accompanied. Women who had five or more pregnancies (adjusted HR = 3.10, 95%CI: 1.28-7.51) or an initial histological diagnosis of CIN II/III demonstrated an independent risk of treatment failure (adjusted HR = 3.14, 95%CI: 1.20-8.19). Being in a stable relationship was a protective factor against treatment failure (adjusted HR = 0.47, 95%CI: 0.24-0.89). A history of more frequent pregnancies and a histological diagnosis of CIN II/III are directly correlated with risk of CIN treatment failure, whereas being in a stable relationship is inversely correlated with this risk.

Cervical Intraepithelial Neoplasia; Therapeutics; Cohort Studies

Resumo

O objetivo do estudo foi determinar a dinâmica da lesão intraepitelial cervical (NIC) em mulheres tratadas que foram acompanhadas em uma coorte durante dois anos. Foi calculada a probabilidade condicional de falha usando o método de Kaplan-Meier e foram calculadas as hazard ratios *(HR) bruta e ajustada para o risco de falha usando a regressão de Cox com valor de p de entrada < 0,05. Das 237 mulheres que foram tratadas, 51,5% foram acompanhadas por 24 meses e 21,9% delas tiveram falha no tratamento, apresentando recidiva da lesão cervical. Mulheres que tinham mais que cinco gestações (HR = 3,10; IC95%: 1,28-7,51) ou histológico de NIC II/III demonstraram risco independente para falha no tratamento (HR = 3,14; IC95%: 1,20-8,19) e estar em um relacionamento estável mostrou ser um fator de proteção para falha de tratamento (HR = 0,47; IC95%: 0,24-0,89). A história de maior número de gestações e histológico de NIC II/III estão diretamente correlacionados com o risco de falha no tratamento, enquanto que estar em um relacionamento estável é inversamente correlacionado ao risco.*

Neoplasia Intraepitelial Cervical; Terapêutica; Estudos de Coortes

http://dx.doi.org/10.1590/0102-311X00164913

Introduction

Cervical cancer is the second-most common neoplasia in women and is responsible for 15% of all cancers in women, representing approximately 500,000 new cases and 230,000 deaths per year worldwide [1,2].

In Brazil, cervical cancer rates differ between regions, with estimated incidence rates in 2012 ranging from 15/100,000 women in the Southeast Region to 24/100,000 in the North Region. This type of cancer has the highest incidence rate among women in the Amazon region [3]. The mortality rate associated with this neoplasia is also higher in the Amazon region, at 13.07/100,000 women and 16.95/100,000 women in the city of Rio Branco, Acre State, Brazil. In the Southeast and South regions, the estimated mortality rates are 10.32/100,000 and 5.82/100,000 women, respectively (DATASUS. *Mortalidade Hospitalar por Residência: Taxa de Mortalidade por Câncer de Colo do Útero, 2011*. http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sih/cnv/nrac.def, accessed on 02/Mar/2012).

The human papilloma virus (HPV) infection is well known as a necessary, but not sufficient, risk factor for cervical cancer development [4,5]. A set of co-factors is necessary in order for the cancer phenotype to arise, such as age, tobacco smoking, oral contraceptive use, immunosuppression, and host genetic susceptibility [5]. The normally slow development of cervical cancer allows for the identification of precancerous symptoms, classified as low grade (cervical intraepithelial neoplasia – CIN I and HPV during histological examination) or high grade (CIN II/III during histological analysis) according to the probability of progression to cancer [6]. The main public health strategies to control cervical cancer development are screening through the Pap test and the excision of diagnosed lesions by LEEP (Loop Electrical Excision Procedure). However, the risk of treatment failure may vary from 5%-36% worldwide [7,8,9,10].

Therefore, establishing an effective cytological screening program is an important method for cervical cancer control. However, implementing this program has been difficult in the Brazilian Amazon region, for a number of reasons including insufficient population coverage, poor quality of samples sent for examination, poor accuracy of the Pap smear test, lack of cervical intraepithelial lesion treatment, lack of follow-up, and treatment failure [11].

Because Pap smear coverage rates are high in the target population (85.3%) [12] of Rio Branco, a city in the Brazilian Amazon, this community is a good source of information for understanding and identifying factors that may correlate with the quality of cervical cancer screening in this region. Thus, this study sought to determine the epidemiological profile of women who were cytologically diagnosed with cervical intraepithelial lesions from 2007 to 2008 and subsequently treated in the public health system of Rio Branco. We also evaluated these patients for the two years following any treatment performed, taking into account behavior-outcome relationships and factors associated with the recurrence of cervical intraepithelial lesions.

Methods

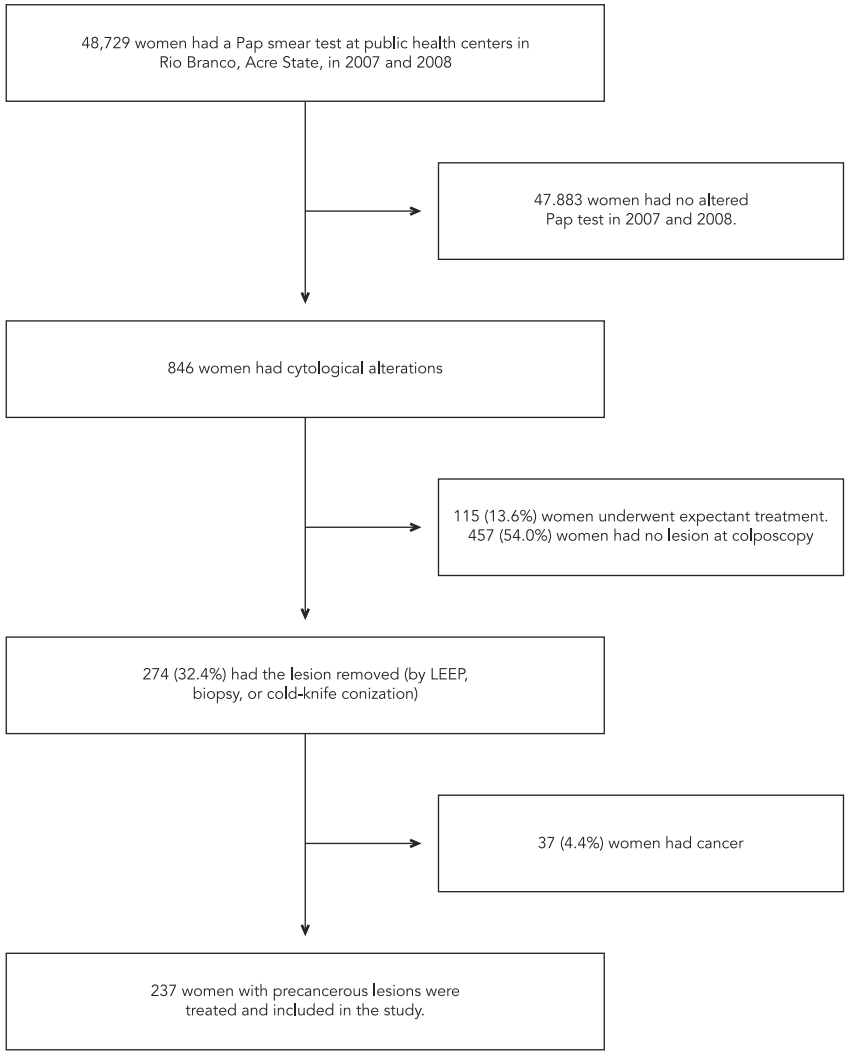
This was a retrospective cohort study of women diagnosed with precancerous cervical lesions by Pap smear and reported to the Cervical Cancer Control Program (Programa de Controle de Câncer de Colo de Útero – PCCCU) in the city of Rio Branco. Data from the Cervical Cancer Information System (Sistema de Informação do Câncer de Colo do Útero – SISCOLO) in 2007 and 2008 were used as the source of this population study. In the state of Acre, all Pap test and histological slides are processed and analyzed in the same national public health Pathology laboratory (central pathology of Acre), which follows the Bethesda System to classify both cytological and histological exams as low grade (CIN I and compatible with HPV cytopathic effect during histological examination) or high grade (CIN II/III during histological analysis) [13].

During 2007 and 2008, 48,729 women had a Pap smear test at public health centers in Rio Branco. Women who were screened for cervical cancer in Rio Branco were identified by SISCOLO. A total of 846 women had cytological alterations during those two years, 274 (32.4%) of which had the lesion removed (by LEEP, biopsy, or cold-knife conization). Of these, 37 (4.4%) of the women had cancer and were therefore excluded from this cohort; the remaining 237 women with precancerous lesions were treated and accompanied for 24 months in this study (Figure 1).

Following lesion removal, the medical records of those with cytopathological changes were obtained from the Acre Cancer Control Center (Centro de Controle Oncológico do Acre – Cecon) and the basic health units ("unidades básicas de saúde" – UBS). Medical records were identified by name, birth date, mother's name, and the identification number of the abnormal exam. Data were extracted using a standardized form that had been specifically designed for this purpose.

Figure 1

Flowchart for selection of the study population. Rio Branco, Acre, Brasil, 2007-2008.



Variables for the following areas were collected: sociodemographic (age, marital status, and education level), epidemiological (smoking, age at first sexual intercourse, number of sexual partners, and oral contraception use), clinical (first histological exam, months of follow-up, cytology and treatment failure), and quality of screening and treatment (follow-up time in months and treatment performed).

Education level was classified as uneducated or number of years of school completed. Smoking was classified as never smoked, former smoker, or current smoker. The cytopathological and histopathological results were classified using the Bethesda System, which was established in 2001 and classifies lesions as low grade (HPV and CIN I) or high grade (CIN II and CIN III) based on histology.

The criteria used in this study for evaluating the quality of cervical lesion screening and treatment were designated by the Ministry of Health, which recommends that low grade lesions should be reevaluated by cytology after six months. All repeat or high grade lesions should

immediately be recommended for colposcopy at a middle complexity unit to verify the lesion. All patients with cervical cell changes who underwent lesion removal should be monitored for two years.

Time zero (T0) for this cohort was the date of removal of the precancerous lesion, and follow-up time (ΔT) was the time from T0 until the last cytological test identified in the 24 months of monitoring.

Any change in the CIN or identification of atypical squamous or glandular cells within the 24-month follow-up period was considered a failure. Women whose cytology remained clear up to the end of the study, who moved to another city, did not return to the unit for follow-up cytology, were censored on the date of the last visit. When this classification was due to loss of follow-up, the date of the last cytological exam was used.

To estimate the conditional probability of failure post-treatment after 6, 12, and 24 months of follow-up, we used Kaplan-Meier statistics. To evaluate differences in these conditional probability of failure curves, the 95% log-rank test was used.

To evaluate the risk factors associated with treatment failure, the Cox proportional hazards regression model was used to estimate the raw and adjusted hazard ratios with their respective 95%CI (95% confidence interval). The final model was constructed to evaluate prognostic factors of treatment failure. Independent variables that demonstrated statistical significance by univariate analysis were included in the Cox multivariate regression model, with p-value < 5% for entry and p-value > 10% as the exclusion criteria for the model. Data were organized in Excel 2010 (Microsoft Corp, USA) and analyzed in SPSS 13.0 (SPSS Corp., Chicago, USA). This project was approved by the research ethics committee at the Federal University of Acre (Universidade Federal do Acre – UFAC).

Results

From 2007 to 2008, 237 women had precancerous lesions and underwent treatment, constituting the studied cohort. Women were monitored for an average of 18 months, while 122 women (51.5%) were monitored for 24 months. Of the women followed, 52 (21.9%) had a new lesion after treatment.

Other factors were as follows: 67.5% of the treated women were between 25 and 45 years old, 71% finished elementary school, 38% were smokers, and 90.9% used contraception. Approximately half of the women were classified as single (54.5%), 31.3% became sexually active before 14 years of age, and 67.8% had had more than three pregnancies (Table 1). Histology revealed that 31.9% of lesions were HPV-positive, 22.4% were CIN I, and 45.7% were CIN II or CIN III.

The conditional probability of treatment failure at 24 months in women who were not in a stable relationship was 44.4% (L-R p-value = 0,025), having more than five pregnancies also increased the risk of failure at 24 months (52.9%, L-R p-value = 0,005). Also, women presenting histological diagnostic compatible with HPV cytopathic effect, CIN I, and CIN II/III presented a risk of treatment failure of 22.1%, 35.7%, and 45.5%, respectively (L-R p-value = 0.030), (Table 1).

Women who had had more than five pregnancies had a 3.10-fold risk of treatment failure compared to women who had had less than five pregnancies; this risk was independent of age, marital status, or histology upon entry. Similarly, women with an entering histological grade of CIN II/III also demonstrated an increased risk of treatment failure with an adjusted hazard ratio of 3.14 (95%CI: 1.20-8.19). Conversely, being in a stable relationship was protective against treatment failure, with an HR of 0.47 (95%CI: 0.24-0.89); this protection was independent of age, marital status, and number of pregnancies. Women who used oral contraception had increased risks for failure, although the estimates were not statistically significant (Table 2).

Discussion

In summary, the present study identified that 67.5% of women treated in the cohort were between 25 and 45 years old, 71% finished elementary school, 38% were smokers, and 90.9% used contraception. Approximately half of the women were classified as single (54.5%), 31.3% became sexually active before 14 years of age, and 67.8% had had more than three pregnancies. Histology revealed that 31.9% of lesions were HPV-positive, 22.4% were CIN I, and 45.7% were CIN II or CIN III. These findings demonstrate the importance of providing adequate follow-up to women from Rio Branco, who have been diagnosed with precancerous cervical lesions.

Women who had had more than five pregnancies and those with entering histological grade of CIN II/III demonstrated an increased risk of treatment failure. Conversely, being in a stable relationship was protective against treatment failure; this protection was independent of age, marital status, and number of pregnancies. Women who used oral contraception had

Table 1

Epidemiological and clinical characteristics of women with cytological alterations and conditional probability of treatment failures. Rio Branco, Acre State, Brazil * (N = 237).

Variable	n (%) **	% treatment failure (months)			
		6	12	24	Log-rank (95%CI)
Age (years)					
< 25	30 (12.7)	0.0	4.0	42.0	
25-45	160 (67.5)	0.7	1.5	31.0	0.149
> 45	47 (19.8)	3.0	6.6	55.5	
Marital status					
Stable union	103 (45.6)	0.0	1.3	25.9	0.025
Not in a stable union	123 (54.4)	1.0	2.0	44.4	
Education					
Illiterate	21 (14.2)	5.0	5.0	59.3	
Up to primary school	84 (56.8)	1.4	4.7	35.4	0.348
> Primary school	43 (29.0)	0.0	2.6	40.8	
Smoker					
Yes	57 (38.0)	2.1	4.2	28.8	0.285
No	93 (62.0)	1.4	2.9	38.8	
First intercourse (years)					
< 14	66 (31.3)	1.8	3.7	43.5	0.085
> 14	145 (68.7)	0.0	0.9	30.7	
Pregnancy					
1-2	68 (32.2)	0.0	1.9	21.7	
3-4	73 (34.6)	0.0	1.9	35.1	0.005
> 5	70 (33.2)	1.8	5.6	52.9	
Oral contraceptive					
No	6 (9.1)	0.0	0.0	0.0	0.248
Yes	60 (90.9)	0.0	1.9	38.8	
Histology at entrance					
HPV cytopatic effect	74 (31.9)	2.0	2.0	22.1	
CIN I	52 (22.4)	35.7	35.7	35.7	0.03
CIN II/III	106 (45.7)	1.1	3.2	45.5	
Follow-up (months)					
6	38 (16.0)				
12	22 (9.3)				
12 to 24	177 (74.7)				
24	122 (51.5)				
Histology of the failure					
CIN I	18 (34.6)				
CIN II	14 (27.0)				
CIN III	20 (38.4)				
Total	52 (21.9)				

95%CI: 95% confidence interval; CIN: cervical intraepithelial neoplasia; HPV: human papilloma virus.

* Kaplan Meier method;

** Total values may vary according to missing values.

increased risk of failure, although the estimates were not statistically significant.

The risk of treatment failure for precancerous lesions and the associated risk factors are criteria that must be analyzed when evaluating the efficacy of cervical cancer prevention and control programs. In this study, a 21.9% failure rate was observed. This finding is consistent with several

Table 2

Hazard ratio (HR) for crude and adjusted for relapse during treatment among women with CIN. Rio Branco, Acre State, Brazil.

Variable	Crude HR (95%CI)	Adjusted HR (95%CI) *
Age (years)		
25	1.00	1.00
25-45	0.60 (0.29-1.27)	0.63 (0.29-1.38)
> 45	1.14 (0.49-2.67)	1.12 (0.46-2.73)
Marital status		
Not in a stable union	1.00	1.00
Stable union	0.55 (0.30-1.00)	0.47 (0.24-0.89)
Education		
Illiterate	1.00	1
Up to primary school	0.61 (0.27-1.34)	0.49 (0.19-1.26)
> Primary school	0.69 (0.28-1.67)	0.50 (0.17-1.48)
Smoker		
No	1.00	1.00
Yes	0.696 (0.33-1.46)	0.80 (0.33-1.77)
First occurance of intercourse (years)		
< 14	1.00	1.00
>14	1.67 (0.92-3.04)	1.56 (0.82-2.96)
Pregnancy		
1-2	1.00	1.00
3-4	1.71 (0.75-3.02)	1.77 (0.73-4.20)
> 5	2.85 (1.35-6.03)	3.10 (1.28-7.51)
Oral contraceptive		
No	1.00	1.00
Yes	22.43 (0.4-38.8)	20.41 (0.4-37.6)
Histology at entrance		
HPV cytopatic effect	1.00	1.00
CIN I	1.50 (0.59-3.81)	1.87 (0.60-5.78)
CIN II e CIN III	2.31 (1.07-5.02)	3.14 (1.20-8.19)

95%CI: 95% confidence interval; CIN: cervical intraepithelial neoplasia; HPV: human papilloma virus.

* Adjusted by marital status, first histology and age.

studies that observed recurrence rates of 5 to 35%, although it is lower than that found in Rio de Janeiro, Brazil (31.7%) [7,8,9,10].

The effect of exposures is additive over time; therefore, age is directly correlated with cervical cancer risk [1,3]. Several studies have shown that women who are older, have high-grade intraepithelial lesions, are black- or brown-skinned, have a history of multiple pregnancies, became sexually active at a young age, have had more sexual partners, or come from a low socioeconomic background are more likely to have cervical cancer and treatment failure [12,14,15,16,17].

Number of pregnancies was one of the factors associated with the highest probability of failure; by 24 months, the probability of failure was 52.9% among women with a history of more than five pregnancies. The literature has shown that multiparity is associated with an increased frequency of cellular changes at the squamocolumnar junction. A higher number of pregnancies is likely correlated with low socioeconomic class, early initiation of sexual intercourse, and greater number of sexual partners [18]. This risk factor is significant, but one that can be addressed by cervical cancer prevention and control programs.

Women who became sexually active early, i.e., before 14 years of age, demonstrated a higher probability of failure at 24 months (43.5%) than women who became sexually active after this age. Our findings corroborate a study conducted in the United States, in which Hunter et al. [19]

reported that early initiation of sexual activity (before 16 years of age) was a risk factor for cervical cancer. The authors proposed that women who become sexually active at a young age are more likely to have multiple partners and, therefore, multiple HPV infections. The squamocolumnar junction may also be more vulnerable to HPV infection at a young age, when immunity is not completely developed [19].

Women demonstrating histological changes consistent with CIN II and CIN III had a significantly higher probability of treatment failure at 24 months (45.5%). Multivariate analysis also revealed a statistically significant risk of failure in women with CIN II/III (adjusted HR = 3.14; 95%CI: 1.20-8.19), independent of age, marital status, and number of pregnancies. This increased risk may reflect that more severe lesions have dysplastic cells in at least two-thirds of the epithelial thickness, making surgical excision less likely to succeed.

In a study of a hospital cohort in Rio de Janeiro, Silva et al. [14] also found that women with a histological diagnosis of CIN II or CIN III had a 28% chance of failure compared to women with CIN I/Metaplasia. The authors also identified a higher risk in women over the age of 50, women who had smoked for more than 10 years, and women who had more than four sexual partners in their lifetime.

Our study suggests that being in a stable relationship protects against treatment failure because women who were not in a stable relationship had a 44.4% probability of failure at 24 months, while women in a stable relationship had a probability of only 25.9% during the same time period. The difference between curves was statistically significant. In addition, multivariate analysis resulted in a hazard ratio of 0.47 (95%CI: 0.24-0.89) for women in a stable relationship compared to single women. This decreased risk may reflect the lower probability of having multiple partners among women in a stable relationship, thereby reducing opportunities for multiple HPV infections [18].

This study also benefited from its location in the Brazilian Amazon, which has the highest cervical cancer incidence and mortality rates in the country. To the best of our knowledge, this study is also the first conducted in the state of Acre, allowing us to assess the state's cervical cancer screening and prevention program.

Conclusions

These findings reinforce the need to implement socio-educational interventions that address cervical cancer risk factors in women from Rio Branco, including lectures and other educational activities that emphasize the influence of the number of pregnancies, age of first sexual intercourse, having a stable sexual partner, smoking, and preventive exams.

Resumen

El objetivo del estudio fue determinar la dinámica de las lesiones intraepiteliales de cuello uterino (NIC) en mujeres que fueron tratadas dentro de una cohorte, cuyo seguimiento se realizó durante dos años. Se calculó la probabilidad condicional de error, utilizando el método de Kaplan-Meier y se calcularon los cocientes de riesgo (HR) crudos y ajustados por el riesgo de fracaso mediante la regresión de Cox con el aporte valor p < 0,05. De 237 mujeres que recibieron tratamiento, el 51,5% fueron seguidas durante 24 meses y en el 21,9% fracasó el tratamiento, mostrando la repetición del daño cervical. Las mujeres que tenían más de cinco embarazos (HR = 3,10; IC95%: 1,28-7,51) o NIC histológico II/III mostraron un factor de riesgo independiente para el fracaso del tratamiento (HR = 3,14; IC95%: 1,20-8,19) y estar en una relación estable resultó ser un factor protector para el fracaso del tratamiento (HR: 0,47; IC95%: 0,24-0,89). La historia de embarazos múltiples y con diagnóstico histológico NIC II/III se correlaciona directamente con el riesgo de fracaso del tratamiento, mientras que si está en una relación estable se correlaciona inversamente con la relación riesgo.

Neoplasia Intraepitelial del Cuello Uterino; Terapéutica; Estudios de Cohortes

Contributors

P. R. Prado, R. J. Koifman and I. F. Silva designed, wrote, revised, and approved the study.

Acknowledgments

The authors thank Capes through the joint venture established between the Federal University of Acre (UFAC – Public Health Graduate Program) and the Graduate Program in Public Health and the Environment (ENSP/Fiocruz), as well employees from Cecon/Acre for their assistance with this research.

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Submitted on 17/Sep/2013
Final version resubmitted on 19/Feb/2014
Approved on 21/Feb/2014