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Incidence of cervical cytological abnormalities following a negative smear result in an opportunistic screening scenario: A cohort study

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ABSTRACT

Objectives: To analyse the incidence of atypical cells and their risk factors in an opportunistic screening context.
Study design: This cohort study with passive follow-up is based on analysis of 86,609 women living in Maranhão State - Brazil, who had a negative cervical cytological test recorded in the Cervical Cancer Information System (SISCOLO) in 2007 and who had at least 1 follow-up test up to 31 December 2012. The cumulative incidence (CI) and incidence rate (IR) of low grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesions and cancer (HSIL+) were calculated. A Cox regression model was used to identify independent factors associated with the risk of presenting atypical cells.
Results: At 60 months follow-up the CI of LSIL reached 10.7 per 1000 and that of HSIL + was 3.9 per 1000. LSIL and HSIL + IRs were 334.7 and 120.3 per 100,000 person-years (PYs), respectively. LSIL and HSIL + occurred in 65.0% and 57.3% of women <3 years after the study entry, respectively. The risk of presenting HSIL + increased when a previous cervical cytological test had not been performed, with advancing age and when the Municipal Human Development Index (MHDI) decreased.
Conclusion: This study highlights a significant tendency towards increased IR and risk of presenting HSIL + as MHDI decreased.

Introduction

Cervical cancer (CC) in Brazil is still a major public health problem. The estimate for 2019 is 16,370 new cases with an estimated risk of 15.43 cases per 100,000 women, representing the third most common cancer in Brazil's female population [1]. The country's mortality rate for this cancer adjusted by the world's population in 2015 was 5.13 per 100,000 women, being the leading cause of death in some regions [2]. In some rural areas and cities outside the capitals of North and Northeast Brazil, mortality rates are increasing [3].

In the State of Maranhão, located in Northeast Brazil, over the years, data have shown CC has been the most frequent gynaecological cancer, with incidence rates ranging from 16.65/100,000 in 2007 to 23.60/100,000 in 2012 [1], an increase of 42%. Between 2007 and 2012 the State of Maranhão ranked second in the country for mortality (adjusted mortality rate 10.02/100,000) [2].

This information follows a world trend in which a higher incidence of and mortality from this cancer has been identified in socioeconomically less favoured regions [3]. A total of 69.7% of new cases and 74.9% of deaths from CC occur in less developed countries with a medium or low Human Development Index (HDI) [4]. Maranhão ranks second to last for Brazilian states in HDI ranking [5]. In this scenario, the high incidence and mortality from CC arises from poor living conditions with a lack of or difficult to access health services, especially to organised population screening programs [6,7].

In Brazil, the CC screening programme is based exclusively on opportunistic conventional Pap smears [8]. According to the Brazilian guidelines [8], cervical cytological tests should be offered to women with an active sex life, primarily those in the 25- to 64-year age group, with a 3-year interval following 2 consecutive normal tests 1 year apart.

Knowledge of risk and time to onset of precursor cytological changes or suspected CC after a negative screening is very important in terms of filling this gap. This study will evaluate

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the incidence of atypical cells and their determinants in the context of opportunistic screening based on cytological tests.

Methods

A cohort study was performed with passive follow-up. The cohort consisted of: 1) all women aged 25 to 59 years, 2) negative cervical cytological test results from smears collected between 01 January and 31 December 2007, 3) at least 1 follow-up cervical cytological test performed before 31 December 2012, and 4) the recorded results of both tests in the Cervical Cancer Information System (in Portuguese: Sistema de Informação do Câncer do Colo do Útero - SISCOLO). A total of 89,762 women with negative cytological tests were identified in 2007 and were followed up regarding atypical cell development for up to 60 months. A total of 3153 women were excluded (3.5%) because they had a subsequent test less than 6 months before they entered the study. Follow-up began on the date of the first negative cytological test (*i.e.*, with the absence of any cytological lesions) and ended on the date of the first positive test for low grade squamous intraepithelial lesion (LSIL) or high-grade squamous intraepithelial lesions and cancer (HSIL+). In cases in which LSIL and HSIL + were not observed, follow-up ended on the date of the last negative cytological test. No patient presented a diagnosis of LSIL and HSIL + simultaneously. The follow-up time ranged from 6 to 60 months (mean = 3.2 ± 1.5).

SISCOLO was developed by the Brazilian Ministry of Health to assist in the reimbursement for cervical cytological tests and to monitor and evaluate the National Programme for the Control of Cervical Cancer activities. The Health Department of Maranhão State made the SISCOLO database available for this research in electronic form.

As SISCOLO records each test and does not have a unique "key" for identifying the woman, the Reclink software version 3 [9] was used to establish a relationship between the databases to identify women who repeated the test in the follow-up period. Details of the method used can be found in Girianelli et al. [10].

The following SISCOLO variables were analysed: age in years on the date of the cytological test collection, history of undergoing a prior screening test and time since the last screening test. The cervical screening results were classified according to the Brazilian Nomenclature for Cervical Reporting [11], an adaptation of the Bethesda System adopted in the country since April 2006 on the recommendation of the Ministry of Health. In this study, "atypical cells" were considered cytological reports classified as LSIL (including cytopathic effect compatible with Human papillomavirus (HPV) - cytopathic effect by human papillomavirus - and cervical intraepithelial neoplasia I (CIN I), HSIL (including CIN II and CIN III) and suspected squamous or glandular cancer lesions (including HSIL and not excluding micro-invasion, invasive squamous cell carcinoma, adenocarcinoma in situ, invasive cervical adenocarcinoma, invasive endothelial adenocarcinoma and not otherwise specified [NOS] invasive adenocarcinoma). For data analysis purposes, HSIL and suspected squamous or glandular cancer lesions were referred to as HSIL + . The Municipal Human Development Index (MHDI) of the woman's area of residence was used. The MHDI is an adaptation of the global HDI methodology, adjusted for national indicators [5]. The municipalities were classified as high MHDI (0.700 to 0.799), medium MHDI (0.600 to 0.699), low MHDI (0.500 to 0.599) and very low MHDI (0.400-0.499). The percentage of LSIL and HSIL + detected within 3 years of study entry in relation to MHDI was calculated.

The research project was approved by the Research Ethics Committee of the Federal University of Maranhão (Universidade Federal do Maranhão) Nº 045181/2013, as per the National Council of Health Resolution number #466/2012. Informed consent was not necessary due to secondary use of health data.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics software, version 20. Categorical variables were presented as absolute and relative frequencies and continuous variables as the mean and standard deviation (SD). First, the cumulative incidence (CI) rate was calculated for LSIL and HSIL + for the entire study period. The incidence rates (IR) of LSIL and HSIL + for the exposure categories were obtained by dividing the number of cases by the total number of person-years (PYs) that contributed to that category. A Cox regression model was used to compare the risk (hazard ratio [HR]) of presenting cellular atypia among the analysis categories. P-values <0.05 were considered statistically significant.

Results

The study included 86,609 women. Follow-up ranged from 6 to 72 months, with a mean of 37.9 months (±18.2). The mean age was 38.2 years (±9.3). Most women had undergone a prior cytological test (63.2%). The time since the last screening was ≤ 2 years in nearly 3/4 of the women (73.9%), and 72.1% lived in municipalities with a medium or low MHDI (Table 1).

Table 1
Initial cohort characteristics and lesions detected throughout the 5-year follow-up. Maranhão.2007–2012.

Variables	n	%
Age group		
25 to 29 years	19,041	22.0
30 to 39 years	31,432	36.3
40 to 49 years	23,298	26.9
50 to 59 years	12,838	14.8
Prior screening test		
Yes	54,708	63.2
No	9,008	10.4
Do not know	11,945	13.8
No information	10,948	12.6
Time since last screening[a]		
<3 years	40,471	73.9
3 years	5,038	9.2
>3 years	4,011	7.3
No information	5,188	9.6
MHDI of municipality of residence		
High	23,786	27.5
Medium	27,982	32.3
Low	34,458	39.8
Very Low	383	0.4
Incident lesions	n	%0[b]
Atypical squamous cells		
Low-grade squamous intraepithelial lesion (HPV and CIN I)	926	10.7
High-grade intraepithelial lesion or worse	329	3.8
High-grade squamous intraepithelial lesion (CIN II and CIN III)	295	3.4
High-grade lesion, not able to exclude micro-invasion	31	0.4
Invasive squamous cell carcinoma	3	0.03
Atypical glandular cells		
Adenocarcinoma in situ	1	0.01
Invasive cervical adenocarcinoma	1	0.01
Invasive endometrial adenocarcinoma	1	0.01
Invasive adenocarcinoma NOS	1	0.01
Any Atypia	85,350	985.5
Total	86,609	

MHDI = municipal human development index; HPV = cytopathic effect by human papillomavirus; CIN = cervical intraepithelial neoplasia; NOS = not otherwise specified.
[a] calculated percentage of total of women who had a prior test (n = 54,708).
[b] per thousand.

Throughout the follow-up period, the diagnosed atypical cytologies were distributed as shown in Table 1. The CI of LSIL and HSIL+ (Fig. 1) reached 10.7 and 3.8 per thousand, respectively.

Most cytological atypia (65.0% LSIL and 57.3% HSIL+) occurred within 3 years of study entry **(**Table 2**).**

A total of 926 LSIL and 333 HSIL + were detected over the 276,703 PYs of observation. The LSIL and HSIL + IRs (Table 3) showed differences in relation to the analysed age groups: while the LSIL rate decreased with age, the HSIL + rate increased. The data also showed as the MHDI decreased, the HSIL + IR increased.

Regarding the risk of having LSIL, both the univariate (Table 4) and multivariate (Table 5) analyses showed as the age increased, the risk of lesions decreased. The absence of prior screening test increased the chance of developing LSIL by 60% (HR = 1.6) (Table 5). As for the MHDI of the municipality of residence, there was a 3.3-fold (HR = 3.3) greater risk of detecting LSIL in the follow-up when the MHDI was very low.

The risk of developing HSIL + was higher in the over 40-year age groups in both the univariate analysis (Table 4) and in the multivariate analysis (Table 5). The absence of prior screening test and more than 3 years since the last test also increased the chance of developing HSIL + . Moreover, as the MHDI decreased, the risk of developing HSIL + increased.

Discussion

The studied population's profile included women who spontaneously approached the Brazilian public health system (in Portuguese: Sistema Único de Saúde - SUS) in the State of Maranhão and whose cytological smears to prevent CC showed no cytological change at baseline. After 60 months of follow-up, the CI of LSIL reached 10.7 per thousand and that of HSIL + was 3.8 per thousand. The IR was 334.7 and 120.3 per 100,000 PYs, respectively.

This study showed that in the vast majority of cases (73.9%), women had tests at an interval shorter than 3 years. Similar results were reported in several Brazilian places with different socioeconomic conditions, such as the city of Rio de Janeiro (74.3%) [12], Baixada Fluminense in the State of Rio de Janeiro (77.3%) [13], the Municipality of Amparo in the State of São Paulo (89.2%) [14], Maceió in the State of Alagoas (68.8%) [12] and Fortaleza in the State of Ceará (72.8%) [15]. Repeating the test in a period shorter than what is recommended did not increase the protective effect of screening [16].

Table 2
Percentage of LSIL and HSIL + detected within 3 years of study entry in relation to MHDI. Maranhão.2007–2012.

MHDI of municipality of residence	LSIL %	HSIL+ %
High	65.6	65.0
Medium	65.6	62.2
Low	63.9	67.8
Very Low	75.0	50.0
Total	65.0	57.3

MHDI = municipal human development index; LSIL = low-grade squamous intraepithelial lesion and HSIL+=high-grade intraepithelial lesion or worse.

Table 3
IR of LSIL and HSIL + according to baseline characteristics of the cohort. Maranhão.2007–2012.

Variables	PYs	LSIL		HSIL+	
		Cases	IR	Cases	IR
Age range					
25 to 29 years	591,22	287	485.4	54	91.3
30 to 39 years	100,249	355	354.1	100	99.8
40 to 49 years	75,907	205	270.1	100	131.7
50 to 59 years	41,425	79	190.7	79	190.7
Prior screening test					
Yes	178,133	545	306.0	203	114.0
No	26,433	112	423.7	44	166.5
Do not know	36,605	161	439.8	36	98.3
No information	35,532	108	304.0	50	140.7
Time since last screening					
<3 years	131,559	411	312.4	164	124.7
3 years	166,14	57	343.1	13	78.2
>3 years	129,26	35	270.8	20	154.7
No information/not applicable	115,604	423	365.9	136	117.6
MHDI of municipality of residence					
High	78,053	297	380.5	61	78.2
Medium	86,039	265	308.0	92	106.9
Low	111,590	352	315.4	176	157.7
Very Low	1,021	12	1175.6	4	391.9
Total	276,703	926	334.7	333	120.3

PYs = person-years; LSIL = low-grade squamous intraepithelial lesion; HSIL+=high-grade intraepithelial lesion or worse; IR = incidence rate per 100,000 PYs; MHDI = municipal human development index.

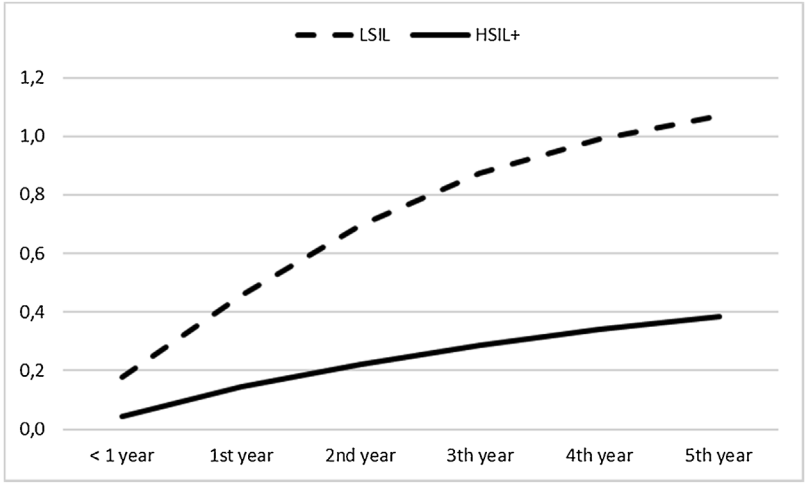

Fig. 1. Cumulative Incidence rate for LSIL and HSIL + over time since the first negative smear result. Maranhão.2007–2012.

Table 4
Univariate analysis of factors associated with the development of LSIL or HSIL + . Maranhão.2007–2012.

Variables	LSIL			HSIL+		
	HR	95% CI	P-value	HR	95% CI	*P*-value
Age range						
25 to 29 years	Ref.			Ref.		
30 to 39 years	0.7	(0.6–0.8)	<0.001	1.1	(0.8–1.5)	0.656
40 to 49 years	0.6	(0.5–0.7)	<0.001	1.4	(1.0–2.0)	0.043
50 to 59 years	0.4	(0.3–0.5)	<0.001	2.0	(1.4–2.9)	<0.001
Prior screening test						
Yes	Ref.			Ref.		
No	1.4	(1.2–1.8)	0.001	1.5	(1.1–2.1)	0.011
Do not know	1.5	(1.3–1.8)	<0.001	0.9	(0.7–1.3)	0.679
No information	1.0	(0.8–1.2)	0.894	1.2	(0.9–1.7)	0.197
Time since last test						
<3 years	Ref.			Ref.		
3 years	1.1	(0.8–1.4)	0.60	0.6	(0.4–1.1)	0.09
>3 years	0.9	(0.6–1.2)	0.38	1.2	(0.8–1.9)	0.40
No information/not applicable	1.2	(1.0–1.4)	0.01	1.0	(0.8–1.2)	0.81
MHDI of municipality of residence						
High	Ref.			Ref.		
Medium	0.8	(0.7–1.0)	0.011	1.4	(1.0–1.9)	0.057
Low	0.8	(0.7–0.9)	0.009	2.0	(1.5–2.6)	<0.001
Very Low	3.3	(1.8–5.8)	<0.001	5.5	(2.0–5.1)	0.001

LSIL = low-grade squamous intraepithelial lesion; HSIL+=high-grade intraepithelial lesion or worse; MHDI = municipal human development index.
Statistically significant values are highlighted in bold.

Table 5
Identification of independent factors associated with the development of LSIL and HSIL + . Maranhão.2007–2012.

	LSIL				HSIL+			
	HR	95% CI		P-value	HR	95% CI		P-value
Age range								
25 to 29 years	Ref.				Ref.			
30 to 39 years	0.7	(0.6	0.9)	<**0.001**	1.1	(0.8	1.5)	0.54
40 to 49 years	0.6	(0.5	0.7)	<**0.001**	1.5	(1.0	2.0)	**0.03**
50 to 59 years	0.4	(0.3	0.5)	<**0.001**	2.1	(1.5	3.0)	<**0.001**
Prior screening test								
Yes	Ref.				Ref.			
No	1.6	(1.1	2.3)	**0.01**	5.1	(2.2	12.0)	<**0.001**
Do not know	1.7	(1.2	2.4)	**0.003**	3.7	(1.5	8.8)	**0.003**
No information	1.2	(0.8	1.7)	0.43	3.8	(1.6	9.0)	**0.002**
Time since last test								
<3 years	Ref.				Ref.			
3 years	1.0	(0.8	1.4)	0.75	0.7	(0.4	1.1)	0.14
>3 years	0.9	(0.6	1.2)	0.36	1.2	(0.7	1.9)	0.49
No information/not applicable	0.8	(0.6	1.1)	0.22	0.3	(0.1	0.6)	**0.002**
MHDI of municipality of residence								
High	Ref.				Ref.			
Medium	0.9	(0.7	1.0)	0.15	1.4	(1.0	2.0)	**0.04**
Low	0.9	(0.7	1.0)	0.12	1.9	(1.4	2.6)	<**0.001**
Very Low	3.6	(2.0	6.5)	<**0.001**	5.4	(2.0	15.0)	**0.001**

LSIL = low-grade squamous intraepithelial lesion; HSIL+=high-grade intraepithelial lesion or worse; MHDI = municipal human development index.
Statistically significant values are highlighted in bold.

A cohort study that evaluated the smears of 41,212 women in Norway also confirmed this result and found that women whose previously negative tests were less than 2 years (RR = 1.0) or 3 years (RR=±0.8) before their current smears did not have a higher risk of developing CIN III than women with a negative Pap smear in the previous year [17]. However, in this study 57.3% of HSIL + and 650% of LSIL occurred in a period of less than 3 years after the negative cytological test.

The IR of precursor lesions and suspected CC in this study (120.3 per 100,000 PYs), notwithstanding the necessary peculiarities, was below that found specifically for CIN III in a previous cohort with similar characteristics. In this study of the Tromsø University Hospital [18] 43,016 women followed-up between 1980 and 1989, the CIN III IRs were 225 per 100,000 PYs among women without cytological evidence of infection and 459 among women with Trichomonas vaginalis infection. In another study by the same

group [17] involving 41,212 women, the CIN III IRs ranged from 202 per 100,000 PYs in women aged 20 to 24 and 396 per 100,000 PYs in women aged 25 to 29. When the time since the last negative test was 3 years or more, the IRs adjusted for age reached 1543 per 100,000 PYs.

Not dissimilarly, the cumulative HSIL + IR (0.384%) recorded in the present study after follow-up was well below that found in other studies with a shorter follow-up. Studies in Rio de Janeiro, with a follow-up of 36 months [19], and Seattle, with a two year follow-up [20], identified CI rates of 1.2% and 3%, respectively. The low sensitivity of the tests performed by the SUS laboratories may have contributed to this situation.

A study based on 10,275,476 tests performed in the Brazilian public health system in 2010, showed that a large number of laboratories had an HSIL percentage of less than 0.4% (the minimum recommended by the Ministry of Health) [21]. More recently, two other regional studies conducted in the states of Paraná (HDI = 0.746) [5] and Minas Gerais (HDI = 0.731) [5], found that almost 80% of the laboratories that performed cytopathological CC screening for the SUS detected a percentage of CC precursor lesions lower than that recommended [22]. One could speculate that there is a strong possibility that precursor changes or suspected CC might not be being identified by the CC screening programme.

The natural history of CC [23] was replicated in the results, demonstrating the progressive character of lesions concomitant to the woman's increasing age. Thus, the age-stratified analysis, confirm what we expected and must result from the fact that LSIL is a transient and self-limiting form of colpocytological change, which is expected to regress spontaneously in most cases [24].

The positive preventive effect was shown very clearly in women who had participated in a screening at least once in their life. In other words, not having previously performed a screening test increased the risk of presenting HSIL + by 5.1 times (HR = 5.1) and the risk of developing LSIL by 60% (HR = 1.6). Although the IR of HSIL + was higher in women whose previous screening test occurred more than 3 years before the time they entered the study, this variable did not demonstrate a statistically significant risk for the development of LSIL or HSIL + . Similarly, a Norwegian study found that women whose previous negative Pap test was 3 or more years prior were not at increased risk of CIN III (RR = 1.3; 95% CI of 0.6–3.2) [17].

In this study, there was a significant tendency towards increased IR and risk of presenting HSIL + as MHDI decreased. demonstrating a strong social inequality in relation to the chances of detecting precursor lesions and suspected CC. Similar studies of HDI association with the risk of cervical cytological abnormalities were not identified, which precluded comparison with the results of this study. However, similarly, the incidence and mortality from CC has been demonstrated to be inversely proportional to HDI [25].

This study has some limitations that must be considered to properly interpret its findings. First, it analysed a secondary database that do not include variables that may be associated with the development of LSIL and HSIL+ (such as sexual behaviour, exposure to HPV, oral contraceptive use and smoking). Another aspect to be considered is that the results of cytological atypia found in smears do not represent the final diagnosis, which is only confirmed after histopathological investigation. The study's strong points include the use of a large database that records all Pap smears performed in the public Programme for the Control of Cervical Cancer in the State of Maranhão. To our knowledge, this study is the first Brazilian study to investigate the incidence of cytological atypia using SISCOLO data. The sample size, the correct search procedures that were adopted and the internal consistency of the observations strengthen the reliability of the results.

In short, the results presented highlight the excessive number of tests performed at intervals of less than 3 years and the fact that the vast majority of cytological lesion diagnoses, including HSIL+, occur less than 3 years after a normal smear screening, even though there is a low incidence of precursor lesions and those suspected of having CC.

Authors' contributions

JRPF, MBCC and LCST participated in the study design, acquisition of data, performed the statistical analysis and interpretation, drafted the manuscript and reviewed and approved the final the manuscript.

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Ethics approval and consent to participate

The research project was approved by the Research Ethics Committee of the Federal University of Maranhão N. 045181/2013, as per the National Council of Health Resolution number #466/2012. Written informed consent was not required due to the observational nature of the study.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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