Research Article

High prevalence of cervical cancer in the Marajó archipelago: an active search study

Abstract

The aim of this study was to estimate the prevalence and risk factors associated with cervical cancer in priority municipalities of the Marajó archipelago. We conducted a study from March 2013 to February 2015 in four municipalities of Marajó. Women were recruited through oral communication. After signing the informed consent form and answering a structured questionnaire the women underwent the Papanicolaou test. The descriptive analyses were performed using frequency distribution and by medians with the standard deviation. The association of risk factors with cervical cancer was evaluated through non-parametric tests. A total of 405 women was included, with a mean age of 40.5 years. The majority had low literacy level and 42% living with a monthly family income below U$ 200. Suggestive results of invasive cervical cancer (ICC) were demonstrated in seven samples, with an overall prevalence of 1.7% and a total of 75 cases of cellular atypia was observed (18.5%). The results of ICC were more expressive between women without full primary education (p=0.0481) and between housewives (p=0,0219). We demonstrated a high prevalence of CC in isolated municipalities of the Marajó archipelago, Brazilian Amazon. Furthermore, the observed prevalence was vastly higher than that found in northern Brazil, which has the most worrisome picture in the country. CC cases were more frequent among women with low literacy level and among those who declared themselves homemakers. Our results emphasize the necessity for improvement of the screening program in the region.

Keywords: epidemiology, uterine cervical neoplasms, amazonian ecosystem, gynecological examination, women

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Introduction

Cervical cancer (CC) is an important public health problem worldwide. The rates of morbidity and mortality are increasing globally, mainly in low-income and lower-middle-income countries that carry most of the burden of CC cases.[1,2] According to the National Institute of Cancer (INCA), CC is the third most incident cancer in the female population of Brazil (non-melanoma skin cancer not considered). However, northern Brazil (Brazil's Amazon basin) is the only region of the country where expected CC cases exceed the number of cases of breast cancer, the most frequent between women in all the others regions. Additionally, the state of Pará was demonstrates the higher number of cases of the region.[3]

The CC is associated with persistent infections by oncogenic types of human papillomavirus (HPV).[4] Some others risk factors like the early onset of sexual activity, multiplicity of sexual partners and tabagism[5] also contribute to the development of the neoplasia. Despite the high prevalence of HPV, only 1% of the infected women progress to CC because the immunologic system is able to eliminate most infections.[6] Nevertheless, the antibodies formed do not protect against new infections throughout life[7] emphasizing the importance of the screening test (Pap test) for the identification of precancerous lesions of the uterine cervix.

An effective CC screening program allows the detection of precancerous lesions and promotes elevated cure rates. Beside of this, CC presents a high survival rate in 5 years, behind only non-melanoma skin cancer.[8] The low Pap test coverage of women in eligible age (25 to 64 years) is the main cause of the unusual high rates of incidence and mortality of CC in northern Brazil, especially in countryside cities.[9] Therefore, the performance of active search in these locations would increase the coverage of the screening test and reduce the mortality rates.[10]

The Marajó archipelago is located in northern Brazil, Northeast of Pará state, Amazon rainforest, Brazil (Figure 1). It is the largest river-maritime archipelago in the world, with an extension of almost 105.000km². The region of Marajó has one of the worst IDH of Brazil and the municipalities of the archipelago are characterized as low-income settings, composed mainly of rural populations living in the environs of the cities, with a general urban density of 35%.[11] Moreover, the archipelago is formed by rivers and canals that make land access difficult or even impossible, limiting the access to small boats, thus, we promote an active search study to estimate the prevalence and risk factors associated with CC in priority municipalities of the Marajó archipelago.
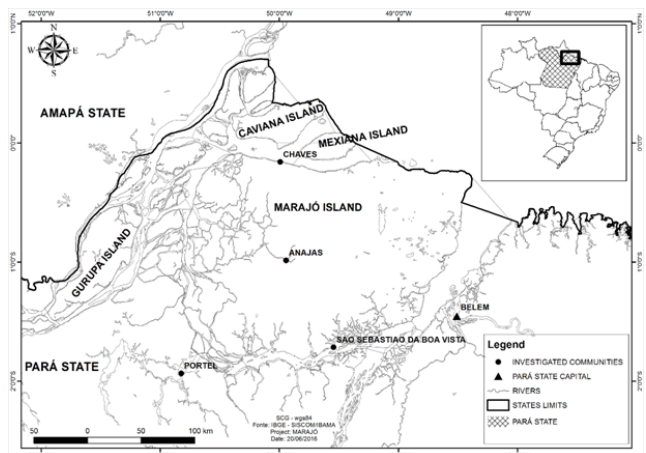

Figure 1 Map of the Marajó archipelago, state of Pará, Northern Brazil.

Material and methods

We conducted an active search study from March 2013 to February

2015 in the municipalities of São Sebastião da Boa Vista, Portel, Anajás and Chaves. The present study integrated the research project "Epidemiological markers in health in the Marajó archipelago" with the approval of the Research Ethics Committee in Human Beings of the Hematology Center of Pará Foundation (protocol nº 30324000-10) and in strictly accordance with the Brazilian ethical guidelines involving human subjects.

An educational intervention visit was made initially in the four municipalities in order to advise about the research objectives, to provide information about the Pap test and to invite the female population to participate in the study. In a second moment, a multi-professional team traveled by boat from Belém (Pará state capital) to the participating municipalities to collecting the samples. All samples were collected by health professionals in collaboration with the health secretary of each municipality. On average, the team performed the collection during one week in each municipality.

All participants signed the Informed Consent Form (parents or legal guardian signature in the case of women under the age of 18) and were instructed to complete the clinical-epidemiological questionnaire. The following variables were investigated: age, conjugal status, occupation/education, household income, age at first sexual intercourse, lifetime number of sexual partners, use of condoms, previous pregnancies, miscarriages and if the Pap test was performed previously. Due to the low screening coverage in the studied region, we included women of all age.

The participants were subjected to a visual inspection of the cervix and the specimens were collected using an Ayre spatula and endocervical brush. Afterwards, Pap smears were fixed in 95% ethanol and stained by conventional Papanicolaou staining. The samples were sent to assessment at the Cytology Laboratory of the Federal University of Pará (UFPA) in Belém, Brazil where they were analyzed by two experienced specialists (discordant cases or suggestive cases of malignancy were discussed with a third specialist). Cytological diagnosis was classified according to the Brazilian Nomenclature for Cervical Cytopathological Reports as normal, inflammatory, atypical squamous cells (ASC), atypical glandular cells (AGC), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial neoplasia (HSIL) or suggestive of invasive cervical cancer (ICC).[12]

We also searched for suggestive characteristics of vaginal infections caused by *Gardnerella sp* (bacterial vaginosis), herpes virus; *Trichomonas vaginalis*, *Candida sp.* and *Chlamydia trachomatis*.

All results were sent to the health secretary of each municipality investigated, who committed themselves to the delivery of the results or for referral of patients to medical care follow up.

The descriptive analyses of the qualitative and quantitative variables were performed using frequency distribution and by medians with the standard deviation (SD), respectively. The association of risk factors with cervical cancer was evaluated through non-parametric tests (Fisher's exact test, G-test) and demonstrated in tables. The amplitude, mean and standard deviation of the ages of women with cervical lesions (LSIL, HSIL and invasive cancer) was evaluated through a Box Plot graphic and the statistic association was performed using the Mann-Whitney U test. All analyses were performed on BioEstat 5 program adopting a two-tailed p-value ≤ 0.05.[13]

Results

Cervical samples were collected from 473 women. Of these, 68 samples were excluded (cell samples not sufficiently preserved; 14.4%), resulting in 405 samples. The participants had a mean age of 40.5 years (SD±14.5, range: 16 to 78), were housewives (57.3%), had low literacy level (not literate or could only read and write) (62.2%) and monthly family income between one and three minimum wages (56.7%) (Brazilian minimum wage - U$ 200/approximately) (another 42% had a monthly family income below a minimum wage). Most (70.4%) were married or had a stable relationship, 58% had less than three sexual partners during lifetime, 65.7% had sexual initiation after the age of 15, 87.8% did not smoke and 51.7% did not use condoms during intercourse. The vast majority (90%) reported at least one pregnancy, with an average of five pregnancies. The occurrence of at least one miscarriage (spontaneous abortion) was reported in 31.9% of participants (mean=1.7; range:1-9).

Suggestive invasive cervical cancer (ICC) was demonstrated in seven samples, with an overall prevalence of 1.7% (7/405). Most ICC cases were suggestive of Squamous Carcinoma (n=6; 86%). According to these results, the estimates of the crude prevalence of ICC were 1728 cases per 100 thousand inhabitants. The overall prevalence of high-grade intraepithelial lesion (HSIL), low-grade intraepithelial lesion (LSIL) and atypical squamous or glandular cells, with no intraepithelial lesion or cancer (included ASC-US, ASC-H, and AGC) were 3,7%, 4.9% and 8.2%, respectively. A total of 75 cases of cellular atypia were observed (18.5%). ICC contributes to 9.3% (7/75), HSIL to 20% (15/75) and LSIL to 26.7% (20/75). The others 44% (33/75) were associated to ASC-US or ASC-H or AGC (Table 1).

Table 1 Classification of cytological results according to the municipalities investigated

Municipality	Normal citology		Inflammatory		ASC-US		ASC-H		AGC		LSIL		HSIL		Squamous cell carcinoma		Adenocarcinoma		Total
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n
São Sebastião da Boa Vista	42	37,8	47	42,3	4	3,6	3	2,7	2	1,8	8	7,2	2	1,8	3	2,7	0	0	111
Portel	30	41,7	27	37,5	5	6,9	3	4,2	0	0	3	4,2	1	1,4	3	4,2	0	0	72
Anajás	40	40,8	29	29,6	8	8,2	4	4,1	0	0	8	8,2	8	8,2	0	0	1	1,0	98
Chaves	59	421	56	45,2	3	2,4	1	0,8	0	0	1	0,8	4	3,2	0	0	0	0	124
Total	171	42,2	159	39,2	20	4,9	11	2,7	2	0,5	20	4,9	15	3,7	6	1,5	1	0,2	405

The ratio between HSIL and ICC cases was 2.1 and the prevalence of potentially malignant lesions (HSIL) or malignancies (invasive squamous cell carcinoma or invasive adenocarcinoma) (n=22) in the municipalities of São Sebastião da Boa Vista, Portel, Anajás and Chaves were 4.5% (5/111), 5.6% (4/73), 9.2% (9/98) and 3.2% (4/124), respectively (p> 0.05). The others 330 samples presented normal cytology (171/405; 42%) or inflammatory results without the identification of the agent (159/405; 39,3%).

The mean age of women with LSIL, HSIL or ICC was 31.6 years (17 to 48), 42.3 years (19 to 60) and 47.5 years (31 to 71), respectively.

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It was demonstrated a statistically difference in the mean age of the groups with LSIL and HSIL (10 years; p=0,0095), LSIL and ICC (16 years; p=0,0018), but not for HSIL and ICC groups (five years; p=0,3733) (Figure 2). The results of ICC were more expressive in women without full primary education (p=0.0481) and in those who declared themselves to be housewives (p=0,0219) (Table 2). There was no statistically significant association with the other risk factors evaluated.

Table 2 Socio-epidemiological and behavioral characteristics associated with invasive cancer in women living in municipalities of the Marajó archipelago

| Variables	Total	Invasive carcinoma	P-valor
	n (%)	n (%)	
Age (years)			0,7087*
≤ 40	217 (53,6)	3 (1,4)	
> 40	188 (46,4)	4 (2,1)	
First Pap smear test			0,3297*
Yes	81 (20)	3 (3,7)	
No	324 (80)	4 (1,2)	
Conjugal status			0,1098*
Married	285 (70,4)	7 (2,4)	
Single	120 (29,6)	0	
Number of sexual partners in life			0,1609*
≤ 2	281 (79,2)	4 (1,4)	
> 2	74 (20,8)	3 (4,1)	
Age at first sexual intercourse (years)			0,1008*
< 15	129 (34,3)	0	
≥ 15	247 (65,7)	7 (2,8)	
Condom use			0,7161*
Yes	203 (51,7)	3 (1,5)	
No	190 (48,3)	4 (2,1)	
Cigarette smoking			0,6589**
Yes	49 (12,2)	0	
No	353 (87,8)	7 (13,2)	
Educational level			0,0481
Not literate or could only read and write	252 (62,2)	7 (2,89)	
Basic education or more	153 (37,8)	0	
Housewife			0,0219
Yes	215 (57,3)	7 (3,3)	
No	160 (42,7)	0	
Family income (Number of Brazilian minimum wages1)*			
< 1	170 (42)	4 (2,4)	0,4622
≥ 1	235 (58)	3 (1,3)	
Previous Pregnancy			0,7981**
Yes	365 (90,1)	7 (1,9)	
No	40 (9,9)	0	
Miscarriage			0,4387*
Yes	129 (31,9)	1 (0,8)	
No	276 (68,1)	6 (2,2)	

*Fisher's exact test.

**G-test.

[1]Brazilian minimum wage: U$ 200, approximately.

A total of 81 participants (20%) were undergoing the Pap test for the first time. The mean age was 38 years and the occurrence of ICC was higher among these women (3.7%) when compared to women who had already undergone the screening test (1.2%) (p=0.1646).

It was suggested the presence of bacterial vaginosis in 46% (n=186), candidiasis in 3.5% (n=14), *Chlamydia trachomatis* in 0.2%

(n=1) and *Trichomonas vaginalis* in 0.7 % (n=3) of the evaluated samples.
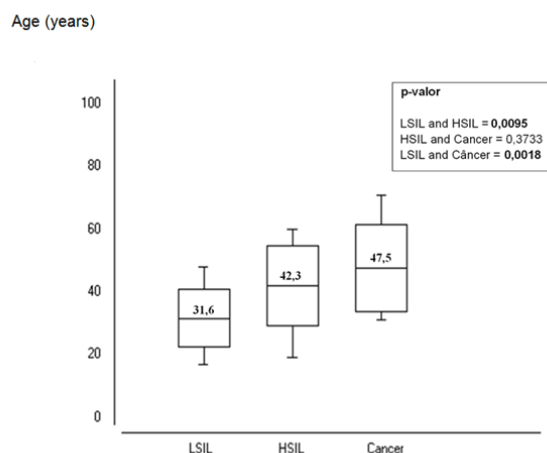
Figure 2 Box Plot of the amplitude, mean and standard deviation of the ages of women with cervical lesions (LSIL, HSIL and invasive cancer), living in municipalities of the Marajó archipelago, State of Pará, Brazil's Amazon basin.

Discussion

The present study aimed at the screening of CC among women residing in priority municipalities of the Marajó archipelago through Pap test. Our study showed high rates of CC in females living in communities with difficult access on Ilha do Marajó, in the Brazilian Amazon. Primary health care services face many obstacles in accessing some communities in the interior of the Amazon and perhaps because of this, many female populations are discovered by the CC screening system, which in Brazil is for through the Pap smear test.

Our study population showed an incidence of CC 76 times higher than that estimated for the Northern region of Brazil.[3] This may be associated with the active search promoted in the priority municipalities of Marajó and is also showed in previous studies in isolated regions of the Brazilian Amazon, with a prevalence of CC ranging from nine[14] to 17 times[15] higher than those estimated by INCA. In addition, we observed that ICC/HSIL proportion (1:2.1) was approximately seven times lower than the expected by INCA for the studied region, which means we had far more cases of CC than presumed. In the other words, the lower the result of this ratio, the lower the effectiveness of the preventive program, since a much larger number of HSIL cases are expected to occur compared to cases of ICC.[16]

Several studies established that populations with low coverage of the screening test demonstrate higher CC rates.[15, 17,18] In our study, one fifth of the participants had never performed the screening test (mean age=38 years), these data are in accordance with the 2013 Brazilian Healthy Survey,[19] which placed the state of Pará as the region of Brazil with the highest proportion of women in eligible age who have never performed the screening test. Furthermore, higher frequencies of unscreened women have been demonstrated in some isolated riverside communities from the Marajó region (53-70%),[20,21] highlighting the importance of the active search for the prevention of cancer in regions with similar characteristics.

The progression of cervical lesions is directly related to age.[12] Our results verified that the mean age difference between the groups

with LSIL and ICC was 16 years (p=0.0018). However, when we compared the groups HSIL and ICC, the difference was only five years (p=0,3733). As a not significant p value was obtained when compared HSIL/ICC groups, it is more likely that women with HSIL progress to ICC in an age lower than it was expected to happen. In corroboration, a previous study demonstrated that northern Brazil experienced the highest rate of mortality due CC in women aged 30 to 69 years, which is considered a premature mortality.[22] Moreover, it was also demonstrated that the risk of progression of untreated high-grade lesions to invasive cancer is around 50%.[23] Thus, since HSIL accounted 20% of the atypical cases in our study, the identification and early treatment of these potentially malignant lesions are primordial for the control of the unusual elevated rates of CC.

The participants of our study presented low schooling, low family income, high age and high number of births, which are in agreement with the literature.[24–26] Another important result was the elevated number of miscarriages in the present study, with rates two times higher than that reported previously.[27–29] Furthermore, bacterial vaginosis was the most frequent genital infection in the present study. The inflammation caused by co-infections facilitates the infection by HPV and is related to the occurrence of cervical lesions and to the risk of progression to CC, if untreated.[30] In this way, the identification and treatment of these infections are fundamental for improving the quality of life of these women, mainly due to lack of access to basic health services.

The prophylactic HPV vaccination of girls (9-13 years) could benefit these communities in the future. However, we believe that the vaccination needs to be used in association with a well-established Pap test program for the prevention of CC in low-income settings. Previous studies demonstrated a low adherence to the vaccine in Pará State and the occurrence of multiple infections associated with high-risk non-vaccinal genotypes.[31,32] Therefore, the better knowledge of the epidemiology of these particular regions and the active search for the realization of the Pap test can help reduce CC mortality rates.

We would like to score a few topics of this work. Firstly, due to the isolated geographic location of these communities and the low access to Pap test, we decided to include women who are not in the recommended age for screening in Brazil (25 to 64 years),[12] although the majority (77%) was in the Brazil's eligible age. Secondly, we had an elevated percentage of unsatisfactory samples (14.4%). Professionals from the municipalities surveyed performed the collection of the cytological material and the lack of training may have influenced in this high percentage. Another possibility would be in relation to the long travel time between Belém and the surveyed municipalities, harming the quality of the material. Finally, we recognize that the small sample size represents a potential limitation of our study, although this fact is outweighed by the need for data from isolated regions.

Conclusion

In conclusion, the present study demonstrated a high prevalence of suggestive CC in isolated municipalities of the Marajó archipelago, Brazilian Amazon, indicating a necessity of improvement of the prevention program in these localities. The observed prevalence was higher than that found in northern Brazil, which has the most worrisome picture in the country. Cervical cancer cases were more frequent among women with low literacy level and among those who declared themselves homemakers. The elevated prevalence of CC highlights the importance of measures to improving the life quality of women living in isolated communities in northern Brazil. A screening test with a good coverage, quality and periodicity in addition with an appropriated follow-up of women with injuries should be priority for reducing the morbidity and mortality rates of CC in this region.

Author's contribution

The author's contribution to this research were as follows. Study design and planning: MYT, RI, MSS. Database construction: JDS, BAPP, LMS, MSS. Analysis and interpretation of results: all authors. Writing of the manuscript: RCV, MSS. Critical revision of the manuscript: MYT, RI, MSS. Final approval of the manuscript: all authors.

Conflicts of interest

The authors declare no conflict of interest.

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