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Prevention, diagnosis and treatment of cervical cancer precursor lesions at the Xingu Indigenous Park, Brazil

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Summary

Purpose: To describe the prevention, diagnosis, and treatment of cervical cancer precursor lesions at the Xingu Indigenous Park (PIX) from 2005 to 2006. *Materials and Methods:* Observational, transversal study. The research sample consisted of 503 sexually active women aged 12 years and older. The research was performed in three stages: screening, colposcopy, and surgical treatment by large loop excision of the transformation zone. *Results:* The cytopathological screening coverage was of 99.6%. The rate of cytologic atypia was 11.7%. Together, low-grade squamous intraepithelial lesions (LSILs) and high-grade squamous intraepithelial lesions (HSILs) were observed in 4.6% of the women. The cytological examination returned a sensitivity of 54%, specificity of 97%, a positive predictive value of 88%, and a negative predictive value of 83%. In the anatomopathological examinations of biopsies, the rate of HSILs was 30.2%. The sensitivity of the anatomopathological examination of biopsies was 72.2%, the specificity was 100%, the positive predictive value was 100%, and the negative predictive value was 44.4%. *Conclusions:* Viable strategies for preventing, diagnosing, and treating cervical cancer precursor lesions in women from the PIX include increasing annual coverage of cytopathological examinations, early detection of cervical intraepithelial lesions, and treatment and follow-up of detected cases.

Key words: Cervical intraepithelial neoplasia; Mass screening; Cervical neoplasm prevention; Indigenous health; South American Native Indians.

Introduction

Cervical cancer, the second-most common tumour of women worldwide, occurs primarily in developing countries, affecting the most vulnerable social groups. In Brazil, the expected number of new cases for 2012 is 17,540. In 2009, cervical cancer was the third-leading cause of cancer death in women, with 5,063 deaths [1]. Even in developed countries, it remains a public health concern. In the European Union, 34,000 new cases and over 16,000 cervical cancer-related deaths are reported each year [2].

The human papillomavirus (HPV) is considered cervical cancer's main causal agent [3-5]. The prevalence of HPV infection in Latin American indigenous women is higher than in the rest of the female population [6-13]. This population is also exposed to cofactors that increase cervical cancer risk, including multiple sexual partners, sexually transmitted diseases (STDs), sexual activity at an early age, multiparity, and low socioeconomic status [14-18]. Low access to preventive screening for early detection and treatment of this cancer and its precursor lesions are other important cofactors for cervical cancer risk. The greater exposure of the Brazilian indigenous population to STDs is related to cultural issues of sexuality, the intensification of contact with the non-indigenous population, and the increased frequency and permanence of the indigenous population in urban areas. [19] The scarce access to information and prevention are also significant issues.

Information on the morbidities and mortality rate associated with cervical cancer in indigenous women is limited, and the data on cervico-vaginal cytopathological screening coverage are worrisome. Geographic isolation, the lack of infrastructure, and of specialised diagnostic support and the turnover of health professionals in indigenous areas are obstacles to the development of adequate screening programs. In addition, indigenous women, due to ignorance, shame, cultural beliefs or distrust, often refuse to undergo preventive screening.

According to official figures, the indigenous population of Brazil corresponds to 734,000 people in more than 200 different groups [20]. They are distributed throughout the country in different sociocultural contexts.

Cervical cancer is still barely noticeable in the setting of public health policy. A greater understanding of the epidemiology of this cancer in indigenous Brazilian women is needed. Thus, the aims of this study were to describe a strategy of prevention, diagnosis, and treatment of cervical cancer precursor lesions in women from the Xingu Indigenous Park (Parque Indígena do Xingu, PIX); to analyse their cytopathological examination coverage rate; to measure the prevalence of cytological atypia; and to determine

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the accuracy of cytopathological and anatomopathological examinations of colposcopically directed biopsies during 2005 to 2006.

Materials and Methods

Design, population, and ethical aspects

This was an observational, transversal, retrospective study using data obtained from documents related to preventing, diagnosing, and treating cervical cancer from 2005 to 2006. This research was conducted in the PIX, which is located in the state of Mato Grosso, Brazil, and encompasses an area of 26,420 km². This region is characterised by the biodiversity of the Amazon rainforest. Its total population in January 2006 was 2,299 inhabitants. The research sample consisted of 503 indigenous women aged 12 years and over with a history of current or previous sexual activity. The sample population belonged to seven ethnic groups – Kaiabi, Kamayurá, Yudjá, Kisêdjê, Ikpeng, Trumai, and Waujá – distributed in 35 villages. The inclusion of women as young as 12 was due to their early onset of sexual activity and the cytological atypia previously observed in younger women [21].

This study was approved by the Research Ethics Committee of the Federal University of São Paulo (Universidade Federal de São Paulo, UNIFESP) and by the National Committee for Ethics in Research of the Ministry of Health, as this study focused on an indigenous population.

Strategy

UNIFESP has conducted a health program in the PIX designated the 'Xingu Project' since 1965 [22]. Until 2005, cervical cancer prevention in the PIX had characteristically low cytopathological screening coverage and low regional access to colposcopy and treatment. An increase in the incidence of precursor lesions, with the occurrence of five cervical cancer-related deaths, was observed from 2000 to 2005.

In light of this situation, beginning in 2005, a partnership was developed between the Xingu Project and the Nucleus of Prevention of Gynaecologic Diseases (Núcleo de Prevenção de Doenças Ginecológicas, NUPREV), Department of Gynaecology, UNIFESP. NUPREV is a specialised service in colposcopy and the treatment of cervical cancer precursor lesions. It is affiliated with the Brazilian Association of Pathology of the Lower Genital Tract and Colposcopy, which is affiliated with the International Federation for Cervical Pathology and Colposcopy, offering postgraduate courses with certification in colposcopy.

The data that were analysed were collected over three stages:

1. Cervical cancer screening: October 2005

To identify the population to be screened, individual medical records, which represent an unprecedented collection of demographic information in the Xingu Project, were used. Through these medical records, it was possible to identify the entire PIX population by name, age, gender and village.

Nurses from the Xingu Project with field work experience and training in cytopathological screening collection at NUPREV participated in this stage. Their training included both theoretical and practical collection of cervico-vaginal smears for one month. The nurses and indigenous health agents visited 35 villages in 30 days. The research team used powerboats to visit the tribes. Most villages had a rudimentary health clinic that offered basic care facilities. In the other villages, the authors improvised treatment areas in the homes of the community. In places with no gynaecological table, the cervico-vaginal smear was performed on stretchers.

As a light source, a flashlight fixed to the examiner's forehead was used. Women experiencing their menstrual cycle and in late puerperium were excluded from the study and were evaluated later. Two women were not screened because they lived outside the PIX. All women agreed to undergo a gynaecological examination after talking about the importance of cancer prevention. The authors decided to initiate immediate treatment in cases of vulvo-vaginitis and cervicitis, according to the service protocol.

The gynaecological examination included inspection of the vulva, followed by the introduction of a disposable vaginal speculum to expose the cervix. Exfoliated cells from the vaginal fornix, ectocervix, and endocervix were collected. The material was deposited on a single histological slide, identified, and fixed with a spray solution. This material was placed in individual microscope slide boxes and then sent to the Cytopathology Laboratory of UNIFESP for processing and evaluation. The cytological classification followed the criteria of the Bethesda System 2001 [23].

2. Colposcopy: February 2006

The second stage of this work was to perform colposcopy on the women from the PIX, with the participation of a medical specialist from NUPREV and Xingu Project staff. Women with cytological atypia were subjected to colposcopy and biopsy when necessary. A portable colposcopic device (DF Vasconcelos) with 6X-40X magnifying lenses and blue and green filters was used. A gasoline-powered generator was used as a source of electricity. Women who had been selected for further examinations were transported by boat from the villages to one of three basic health service units with better infrastructures located in the PIX.

During the examination, the vulva and vaginal introitus were inspected by introducing a disposable speculum and exposing the cervix, followed by the application of 3% acetic acid to the cervix and vagina. Subsequently, Schiller's iodine test was used to visualise changes in the cervix and the vaginal wall epithelium. After removal of the speculum, a 5% acetic acid solution was applied to evaluate the vulva, inguino-crural grooves, pubic mound, perineum and the perianal region. In the presence of abnormal colposcopy findings, a biopsy was performed with 4-5 mm Gaylor-Medina type forceps, followed by haemostasis with 50% ferric perchlorate.

A total of 58 women were examined, 43 of who underwent cervical biopsy. One woman was not examined because she lived outside the PIX. After the authors explained the procedure, no women refused to participate. To classify the colposcopic findings, the nomenclature of Barcelona 2002 was used [24]. The biopsy specimens were placed in a vial with 10% formalin solution and were then sent to the Pathology Department of UNIFESP. The results of pathological examinations followed the classification of Richart 1990 [25].

3. Surgery by large loop excision of the transformation zone (LLETZ): May 2006

The third phase of this study consisted of surgical treatment by LLETZ, with the participation of three medical experts from NUPREV and the Xingu Project staff. A total of 20 surgical procedures were performed in the city of Canarana, Mato Grosso, where the women were transported by water, land or air, depending on their place of residence. The surgeries were performed outside the PIX because complications, such as excessive bleeding of the cervix after excision of the transformation zone by LLETZ, have been previously observed among those women. In this way, back-up medical staff members were available in case of emergency.

Table 1. — *Distribution of atypical cytology and colposcopic findings in indigenous women from the PIX, Brazil, 2005–2006.*

Variable		N	%
Cytologic atypia	ASC-US	15	25.4
	ASC-H	12	20.3
	AGC	7	11.9
	LSIL	15	25.4
	HSIL	8	13.6
	CIS	1	1.7
	AIS	1	1.7
Colposcopic findings	Normal	14	23.7
	Abnormal	43	72.9
	Unsatisfactory	1	1.7
	Not performed	1	1.7
Total		59	100.0

ASC-US: atypical squamous cells of undetermined significance;
ASC-H: atypical squamous cells, cannot exclude a high-grade lesion;
AGC: atypia of glandular cells; LSIL: low-grade squamous intraepithelial lesion;
HSIL: high-grade squamous intraepithelial lesion; CIS: carcinoma in situ;
AIS: adenocarcinoma in situ.

Prior to the surgical procedure, colposcopy was performed to confirm and delineate the lesion. A dispersive electrode (neutral plate) was positioned under the patient. Infiltration injection of anaesthetic with vasoconstrictor was applied at three, six, nine, and 12 hours near the outer margins of the transformation zone. The electrosurgical generator was programmed to dispense cutting waves of 40 watts. The appropriate size of electrode loop was chosen depending on the extent of the injury, and a smoke evacuator with a biological filter was used for the surgeries. After cutting and removal of surgical specimens, the device was reprogrammed to dispense coagulation waves of 80 watts using a ball electrode to achieve haemostasis. Ferric perchlorate (50%) was applied to the cervix and the vagina. The surgical specimen was fixed in a polystyrene plate and placed in a vial containing 10% formaldehyde. The patients was counselled regarding postoperative care. The material was sent to the Department of Pathology, UNIFESP.

Patients subjected to surgical treatment were visited in the PIX by the NUPREV staff for cytopathological screening and colposcopy every six months for two years until discharge. No postoperative complications were observed, such as complications related to pregnancy, cervical insufficiency or cervical stenosis. Two patients were referred for further treatment because they required more invasive surgical procedures.

This study was conducted based on the doctoral thesis defended in 2011 at the Department of Gynecology, UNIFESP.

The Statistical Package for the Social Sciences (SPSS, v16.0), was used. Fisher's exact test applied to analyse the results. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated using the interactive statistical software JavaStat). Statistical significance was set at $p < 0.05$.

Results

From a total of 505 indigenous women aged 12 years and older, 503 (99.6%) were subjected to cytopathological examination. The women's ages ranged from 12 to 75 years old, with a median of 25 years. The 12- to 29-year age group represented 61.4% of the sample, and women over 50 years amounted to 12.4%, resulting in a predominantly young population. A total of 59 women (11.7%) exhibited cytological atypia.

Table 1 shows that low-grade squamous intraepithelial lesions (LSILs) and high-grade squamous intraepithelial lesions (HSILs) represented 39.0% of the cases. Two cases (3.4%) had suspected carcinoma in situ and adenocarcinoma in situ, respectively. Among the women subjected to colposcopy, 43 (72.9%) had an abnormal-appearing exam, with predominant acetowhite epithelium in 35 cases (81.4%), and associated images in eight cases (18.6%). One colposcopic examination was considered unsatisfactory due to intense cervical inflammation. One woman did not undergo the test because she no longer resided in the PIX.

With respect to the age-group distribution of atypical cytology, 80.0% of LSIL cases occurred in the 12- to 29-year age group. In the 20- to 49-year age group, HSILs were more frequent (100%). Significant differences were observed in the analysed data (Table 2).

Table 3 shows the accuracy of the cytopathologic smear in relation to the HSIL results from the anatomopathological biopsy examination, which is considered the gold standard. The cytopathologic smear returned a sensitivity of 54%, a specificity of 97%, a positive predictive value of

Table 2. — *Age-group distribution of atypical cytology in indigenous women from the PIX, Brazil, 2005–2006.*

Age group (years)	Cytologic atypia																	
	ASC-US		ASC-H		AGC		LSIL		HSIL		CIS		AIS		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
12 to 19	4	26.7	1	8.3	-	-	7	46.7	-	-	-	-	-	-	12	20.3
20 to 29	6	40.0	2	16.7	2	28.6	5	33.3	3	37.5	-	-	-	-	18	30.5
30 to 39	2	13.3	4	33.3	5	71.4	1	6.7	2	25.0	-	-	-	-	14	23.7
40 to 49	1	6.7	2	16.7	-	-	1	6.7	3	37.5	-	-	-	-	7	11.9
50 to 59	1	6.7	1	8.3	-	-	-	-	-	-	-	-	-	-	2	3.4
> 60	1	6.7	2	16.7	-	-	1	6.7	-	-	1	100.0	1	100.0	6	10.2
Total	15	100.0	12	100.0	7	100.0	15	100.0	8	100.0	1	100.0	1	100.0	59	100.0

Fisher's exact test p=0.028. ASC-US: atypical squamous cells of undetermined significance; ASC-H: atypical squamous cells, cannot exclude a high-grade lesion;
AGC: atypia of glandular cells; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; CIS: carcinoma in situ;
AIS: adenocarcinoma in situ.

Table 3. — *Cytopathologic smear distribution in relation to the results of anatomopathological biopsy examinations in indigenous women from the PIX, Brazil, 2005–2006.*

Cytopathological exam	Anatomopathological exam (biopsy)							
	Chronic cervicitis		LSIL		HSIL		Total	
	N	%	N	%	N	%	N	%
ASC-US	8	42.1	3	27.3	1	7.7	12	27.9
ASC-H	5	26.3	2	18.2	3	23.1	10	23.3
AGC	4	21.0	1	9.1	1	7.7	6	14.0
LSIL	1	5.3	4	36.3	-	-	5	11.6
HSIL	1	5.3	-	-	7	53.8	8	18.6
CIS	-	-	1	9.1	-	-	1	2.3
AIS	-	-	-	-	1	7.7	1	2.3
Total	19	100.0	11	100.0	13	100.0	43	100.0

Fisher's exact test p=0.002. Confidence interval: 95%.
ASC-US: atypical squamous cells of undetermined significance;
ASC-H: atypical squamous cells, cannot exclude a high-grade lesion;
AGC: atypia of glandular cells; LSIL: low-grade squamous intraepithelial lesion;
HSIL: high-grade squamous intraepithelial lesion; CIS: carcinoma in situ;
AIS: adenocarcinoma in situ.

Table 4. — *Distribution of the results of the anatomopathological examinations of the biopsies in relation to the results of the anatomopathological examinations of the surgical specimens in indigenous women from the PIX, Brazil, 2005–2006.*

Anatomopathological exam (biopsy)	Anatomopathological exam (surgical specimen)				Total	
	Chronic cervicitis		HSIL			
	N	%	N	%	N	%
Chronic cervicitis	2	50.0	2	11.1	4	18.2
LSIL	2	50.0	3	16.7	5	22.7
HSIL	-	-	13	72.2	13	59.1
Total	4	100.0	18	100.0	22	100.0

Fisher's exact test p=0.016. Confidence interval: 95%.
LSIL: low-grade squamous intraepithelial lesion;
HSIL: high-grade squamous intraepithelial lesion.

88%, and a negative predictive value of 83%. The results were statistically significant. In the anatomopathological examinations of biopsy samples, 13 cases (30.2%) showed HSILs, and 11 cases (25.6%) showed LSILs.

Among the 43 women who underwent biopsy, 20 (46.5%) were recommended for LLETZ because they presented with HSIL or histological discordance. Two women with atypia (one CIS and one AIS) showed exacerbated results in the cytopathologic smear, with confirmed HSIL upon anatomopathological examination of the surgical specimen. One of these women was subjected to classic cone biopsy surgery, while the other received a total hysterectomy because she presented with concomitant uterine prolapse.

Table 4 shows the accuracy of anatomopathological examinations of the biopsies in relation to the anatomopathological examinations of the surgical specimens. The exam sensitivity was 72.2%, the specificity was 100%, the positive predictive value was 100%, and the negative predictive value was 44.4%. Histological discordance was observed in five cases (27.8%), possibly because the biopsy was performed in an inadequate facility.

Discussion

This is the first study in Brazil that has described strategies for preventing, diagnosing, and treating cervical cancer precursor lesions in the indigenous population. This study adds knowledge to the small amount of existing epidemiological data on the subject. The study population was concentrated mostly in the younger age groups, reflecting the tendency of fast demographic growth in the Brazilian indigenous population [26-29].

The cytopathologic smear coverage reached 99.6% of sexually active women 12 years of age and above. The existence of demographic records, the definition of the target population, the performance of examinations in the villages, the involvement of indigenous health agents, and the efforts of the nursing staff responsible for the organisation of the study were decisive in achieving this high coverage. The scarce information regarding the collection of cytopathologic smears among indigenous women in Brazil shows that the coverage rates are worrisome, ranging from 5.1% to 23.5% [30]. These women face obstacles to accessing preventive screening, with the result that screening is not always available to them [18, 31]. The absence of organised programs for the prevention of cervical cancer in indigenous areas has also been observed.

The few studies on the indigenous population in Brazil report variations in the prevalence of cytologic atypia, from 4% to 22.3% [16-18, 30, 32-33]. This study identified a prevalence of 11.7%, which is higher than that found in the general Brazilian female population, which ranges from 1.1% to 7.8% [34-39]. In European countries, the rate of cytological abnormalities is approximately 3.7% [40]. The present findings suggest a greater rate of abnormal cytology among indigenous women compared to women in the non-indigenous population. Further studies are needed to confirm this hypothesis.

The presence of LSILs in women between the ages of 12 and 14 years reinforces the need to extend preventive actions to very young women. The early onset of sexual activity in indigenous women coexists with the freedom to exchange sexual partners. This population is vulnerable to STDs, especially HPV, because preventive measures, such as condom use, are not common. The inclusion of indigenous women in programs to control the rates of cervical cancer and STDs should be encouraged.

LSILs and HSILs in cytopathologic smears were more prevalent in the 20- to 49-year age group, similar to other

studies [16-18, 36, 39]. Atypical squamous cells of undetermined significance (ASC-US) or atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H) were found in 5.4% of the cytopathological exams. There is no consensus on the optimal prevalence of ASCs; however, experts consider values below 5% acceptable [41]. The results of this study may be associated with intense inflammatory processes, especially in young women, and atrophy in those of older age. Women with ASC-US were treated for inflammation and were subsequently subjected to the new cervico-vaginal smear collection and colposcopy.

Regarding the colposcopic findings, similar data have been reported in the literature; acetowhite epithelium is the most frequent finding in abnormal colposcopies [42].

The sensitivity performance of cytopathologic smears in the PIX was within the parameters described in the literature, although higher rates have been reported [43, 44]. However, the predictive values were high, which suggests a reliable and extensible screening method that can be applied to other indigenous peoples of Brazil.

The accuracy of the anatomopathological examination of biopsies was significant, demonstrating that the cyto-colpohistological correlation was instrumental in the detection of a greater number of cervical cancer precursor lesions.

In the years after this survey, the cervical cancer preventive actions in the PIX were maintained, with greater than 90% cytopathologic smear coverage. There was a reduction in the occurrence of cytologic atypia from 11.7% in 2005 to 6.0% in 2007. The results of the adopted strategies included increased coverage of cytopathologic smears, early detection of cervical intraepithelial lesions, assurance of treatment and follow-up of detected cases, and a reduction in the incidence of cervical cancer and its precursor lesions.

Health workers, especially nurses, play a crucial role in preventive actions and early detection of cervical cancer. These workers are the most involved with indigenous health care in Brazil and can play an important role in the control of this disease among indigenous peoples.

The absence of cervical cancer-related deaths after six years of prevention argues that the program developed in the PIX was effective and reduced both morbidity and mortality from this type of cancer. The participation of experts from UNIFESP was instrumental in the success of this work, which positively impacted the health of indigenous women in Brazil. It is the present authors' belief that universities have an important role to play in indigenous health and that the knowledge gathered in this study can be applied to other contexts.

Cervical cancer and HPV infection are important public health issues that affect indigenous women, requiring intervention to control their incidence. Improving preventative measures and providing immunisation against HPV in this population are priorities.

It is necessary to expand the access of Brazilian indigenous women to preventive cervical cancer screening, providing diagnosis, treatment, and appropriate follow-up. Moreover, it is essential to promote public policies addressing sexual and reproductive health for this population, to improve the information infrastructure, and to develop more comprehensive epidemiological investigations that may reveal the true health status of the population.

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