The impact of a community intervention to improve cervical cancer screening uptake in the Amazon region of Brazil

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INTRODUCTION

Cervical cancer is the second most common neoplasia among women worldwide. The disease burden is higher in the developing world, and it has been estimated that, in the northern region of Brazil, it is the most important cause of cancer-related deaths among women (4.6 per 100,000 women), with an incidence of 16.75 cases per 100,000 women for the year 2006. Specifically for the State of Acre, in the Brazilian Amazon region and one of the smallest states in Brazil, with only 670,000 residents, the mortality rate due to cervical cancer was 4.02 and there were 14.53 new cases for each 100,000 women in 2002. There is a considerable likelihood, however, that these already high figures were greatly underestimated. It is suspected that many cases are inadequately recorded, because the population cannot access health services and their social and economic circumstances are very unfavorable.

Cervical cancer screening programs are based on the detection of pre-invasive lesions, i.e. cervical intraepithelial neoplasia (CIN). Cervical cytological tests (Papanicolaou tests, or Pap smears) are the primary screening tool used in Brazil. However, in order to be effective, cytology-based screening programs necessitate a complex and expensive infrastructure: primary healthcare units to systematically collect the smears, trained professionals, laboratories for slide processing and reading and, finally, professionals capable of dealing with the abnormalities that may be detected.

OBJECTIVE

The purpose of the present study was to estimate the changes in the incidence of pre-invasive and invasive cervical neoplasia that a possible improvement in access to health services would cause, in a small and isolated province of the Amazon region, in northern Brazil.

METHODS

This study was carried out in the city of Cruzeiro do Sul, which is located in the extreme west of the Brazilian Amazon basin, in the State of Acre. It has been estimated that, in 2001, the municipality had 67,441 inhabitants, 52% of them living in rural areas. The city is accessible mainly by river or air transportation, because during the rainy season the main roads to the city remain unserviceable. Illiteracy is very common: approximately 40% of the population cannot read or even sign their own names. Economic development is negatively affected by the region’s geographical position, in the middle of the Amazon forest, and by several concurrent social problems.

COMMUNITY-LEVEL INTERVENTION

Women were recruited through local advertisements, by radio broadcasting and oral communication; the latter was performed by the investigators themselves. To be eligible to enter the study, women had to: a) provide informed consent by signing (or placing their fingerprints on) the informed consent form (which was read out by one of the investigators when the women were unable to read it themselves); b) have a cervix uteri; c) be outside of the bleeding period of the menstrual cycle; d) have not had sexual intercourse or applied vaginal creams over the three days prior to consultations. Women in this last condition were advised to schedule a new appointment in a few days thereafter. Women were excluded if they: a) had undertaken a Pap test during the last year prior to this consultation; b) had undergone cervical cauterization, biopsy or conization during the last year prior to this consultation; c) were pregnant; d) had had cervical neoplasia (any type) in the past.
A total of 2,226 women were enrolled, and consultations were carried out in the primary healthcare units of Cruzeiro do Sul, from April 2003 to July 2004. In addition to the consultations performed for the purposes of this study, another 3,780 routine Pap tests were carried out in Cruzeiro do Sul while the study was underway.

**Consultation routine**

After signing the informed consent form, the women responded to a structured questionnaire and were subjected to pelvic examination, with inspection of the cervix and collection of samples for the Pap test. As a final step, 3.0% dilute acetic acid was applied to the cervix, and the cervix was re-examined using the naked eye. Abnormal results from the cervical inspection or Pap test prompted referral for colposcopy, with possible biopsy or diathermic excision of the transformation zone, depending on the characteristics of the lesion.

**Pap smear**

Pap smears were taken using an Ayre spatula and endocervical brush. They were fixed in 95% ethanol and stained using the modified Papanicolaou method. The final cytological diagnosis was obtained using the Bethesda System, and the results were classified 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 cancer. The cytological slides from smears collected, 2,106 (94.6%) were classified as negative, CIN 1, CIN 2, or CIN 3. Among women with ASC, the cancer incidence rates in the population, and the proportion of cancer cases detected in 12 months, in a remote municipality in the Amazon region. In this intervention study, in comparison with the official historical data and routine screening in Cruzeiro do Sul, a remarkably higher number of abnormal Pap tests were found and many more cases of cancer were detected. It should be noted, however, that invasive cancer detection rates generally exceed the cancer incidence rates in the population.

**Histology**

Biopsy and conization specimens were fixed in 10% phosphate-buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin (HE). Biopsies were analyzed according to the World Health Organization (WHO) criteria and classified as negative, CIN 1, CIN 2, CIN 3 or invasive squamous carcinoma.

**Statistical methods**

Box plot representations of the mean, median and standard deviations of age at diagnosis for each pre-neoplastic or neoplastic lesion were produced. The performance estimators, or the percentages of positive screening tests across different categorical strata, were compared with historical data retrieved from the Brazilian Ministry of Health's database. The cancer detection rate was calculated per 1,000 women screened.

**RESULTS**

The patients' ages ranged from 20 to 83 years (mean: 39.6 years). Of the 2,226 Pap smears collected, 2,106 (94.6%) were classified as negative. The most frequent Pap abnormality was ASC (1.9%), followed by HSIL (1.8%), LSIL (0.7%), AGC (0.6%), squamous cells carcinoma (0.3%) and adenocarcinoma in situ (0.09%).

Cervical inspection revealed abnormalities in 21.2% of the women, and 541 women were examined by means of colposcopy. Abnormal findings from colposcopy were found in 26% of the women that had undertaken the examination, and 55.8% of these women also had a positive Pap test (data not shown).

Visually detectable lesions were found in a few women with negative cytology: six cases of CIN 1, ten of CIN 2 or 3 and one case of cancer. The majority (78.6%) of the women with AGC were found to be free of histologically-confirmed disease, and the same occurred in 63.6% of the women with ASC. Three (6.8%) of the women with ASC had cancer, and 13 (29.6%) of these were diagnosed with CIN 2 or 3. Among women with LSIL, six (37.5%) were diagnosed with CIN 2 or 3. The proportion of women with histologically-confirmed disease was even higher among women with HSIL, since 81.1% of them had CIN 2 or worse. All the women with Pap smears suggestive of cancer did indeed have high-grade disease (Table 1). The majority (69.4%) of the CIN cases occurred in women below 40 years of age, and disease severity increased in parallel with age (Figure 1).

The proportion of cytology abnormalities in this series was 40% higher (ratio: 1.40) than what has been officially reported for the city of Cruzeiro do Sul. However, during the intervention period of the study, the number of HSIL or worse Pap tests was four times higher (ratio: 4.1) than the official historical figures, and the proportion of cancer cases detected in the population was nine times higher (ratio: 9.3) than what was observed from routine screening (Table 2).

**DISCUSSION**

The primary purpose of this study was to evaluate the consequences of a community-based intervention for the screening of women who had not had a Pap test over the preceding 12 months, in a remote municipality in the Amazon region. In this intervention study, in comparison with the official historical data and routine screening in Cruzeiro do Sul, a remarkably higher number of abnormal Pap tests were found and many more cases of cancer were detected. It should be noted, however, that invasive cancer detection rates generally exceed the cancer incidence rates in the population.
because some cancers would remain asymptomatic in the absence of screening. In the present series, the cancer detection rate (4.49 cases per 1,000 women screened) was 30 times higher than the officially estimated incidence of the disease in Cruzeiro do Sul (14.53 per 100,000 women).3

In countries where the female population is screened appropriately, it has been estimated that less than 1% of Pap smears should harbor a cytological abnormality.4,5 In the present study, 5.4% of the Pap smears were considered to be abnormal. This can be attributed to inadequate previous screening (if any), and to the criterion of only including women who had not had a Pap test during the 12 months prior to enrollment. In addition, the personnel involved in the study were well-trained and performed rigorous quality control at all stages of the screening, from recruiting the women to their treatment.

In alignment with the high rate of Pap abnormalities found in this study, 21.2% of the women also had abnormalities in their cervix that were visible to the naked eye. In India and some African nations, investigators have analyzed the possible role of visual inspection of the cervix with acetic acid (VIA), alone or in combination with Pap smears, as a screening tool. In one of these studies, reporting on 2,754 women, 29.4% of the subjects aged 35-39 years old had abnormal findings from VIA, while this rate decreased to 23.4% in women aged 50-65 years.6,7

High sensitivity is probably the most desirable feature in a screening test. The sensitivity of Pap smears, when the test is performed under ideal conditions (i.e. adequate collection, slides immediately fixed and experienced cytopathologists) barely exceeds 70%.8,9 On the other hand, it is also desirable that the number of false-positive results be reduced to a minimum, thereby avoiding unnecessary referrals for colposcopy. It has been well established that colposcopy places a heavy burden on healthcare systems, because it can only be performed by trained physicians, thus restricting its usage in underdeveloped regions. In the present study, abnormal colposcopy findings were present in 55.8% of the women who had altered Pap smears. However, it has to be mentioned that, in contrast with the expected figures, the number of women with high-grade disease was exceptionally high. The correlation between Pap smear abnormalities and the real presence of cervical disease is not very favorable for low-grade cytological findings. In the ASCUS-LSIL Triage Study (ALTS), only 15% of women with ASC were diagnosed with significant histological lesions, and 50% of those with LSIL had abnormal cervical patterns visible via colposcopy.7

It is unreasonable to suppose that the cervical cancer screening deficiencies in the remote and impoverished regions of Brazil could be resolved in the short term. Cytology-based screening programs demand expensive and complex infrastructure. In addition, Pap smears do not yield results immediately, which is especially problematic in sparsely populated regions with severe transportation shortcomings, like most of the Brazilian Amazon region.

As reported and well discussed in previous Indian, African and even Brazilian reports, VIA might be an acceptable alternative to cytology in low-resource settings with high incidence of cervical neoplasia, considering the logistic and economic circumstances usually encountered in such regions. This is certainly the case in the geographic region where the present study was conducted. For instance, as advocated by Sankaranarayanan et al., VIA allows diagnosis and treatment of cervical abnormalities on a single occasion. This would clearly help overcome one of the main problems in the Amazon region: the huge distances between settlements

### Table 1. Final diagnoses from the cytology results of 2,226 women screened for cervical cancer

<table>
<thead>
<tr>
<th>Histology</th>
<th>Neg</th>
<th>AGC</th>
<th>ASC</th>
<th>LSIL</th>
<th>HSIL</th>
<th>In situ</th>
<th>Invasive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasia absent</td>
<td>2,089 (91.2)</td>
<td>11 (78.6)</td>
<td>28 (63.6)</td>
<td>7 (43.8)</td>
<td>7 (18.9)</td>
<td>0</td>
<td>0</td>
<td>2,142 (96.2)</td>
</tr>
<tr>
<td>CIN 1</td>
<td>6 (0.28)</td>
<td>0</td>
<td>0</td>
<td>3 (18.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9 (0.4)</td>
</tr>
<tr>
<td>CIN 2</td>
<td>3 (0.14)</td>
<td>1</td>
<td>4 (9.1)</td>
<td>4 (25.0)</td>
<td>4 (10.8)</td>
<td>0</td>
<td>0</td>
<td>15 (0.7)</td>
</tr>
<tr>
<td>CIN 3</td>
<td>7 (0.33)</td>
<td>3 (21.4)</td>
<td>9 (60.5)</td>
<td>2 (12.5)</td>
<td>24 (64.9)</td>
<td>0</td>
<td>3 (42.9)</td>
<td>48 (2.2)</td>
</tr>
<tr>
<td>In situ adenocarcinoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2.7)</td>
<td>1 (50.0)</td>
<td>0</td>
<td>0</td>
<td>2 (0.09)</td>
</tr>
<tr>
<td>Invasive squamous carcinoma</td>
<td>1 (0.05)</td>
<td>0</td>
<td>3 (6.8)</td>
<td>0</td>
<td>1 (2.7)</td>
<td>0</td>
<td>4 (57.1)</td>
<td>9 (0.4)</td>
</tr>
<tr>
<td>Invasive adenocarcinoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (50.0)</td>
<td>0</td>
<td>0</td>
<td>1 (0.04)</td>
</tr>
<tr>
<td>Total</td>
<td>2,106 (100.0)</td>
<td>14 (100.0)</td>
<td>44 (100.0)</td>
<td>16 (100.0)</td>
<td>37 (100.0)</td>
<td>2 (100.0)</td>
<td>7 (100.0)</td>
<td>2,226 (100.0)</td>
</tr>
</tbody>
</table>

Neg = negative, AGC = atypical glandular cells, ASC = atypical squamous cells, LSIL = low-grade squamous intraepithelial lesion, HSIL = high-grade squamous intraepithelial neoplasia, CIN = cervical intraepithelial neoplasia.

### Table 2. Screening performance estimators for cervical cancer

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Number of tests in target population</td>
<td>2993</td>
<td>2226</td>
</tr>
<tr>
<td>Percentage of screening tests with positive results</td>
<td>3.9</td>
<td>5.4</td>
</tr>
<tr>
<td>Percentage of screening tests positive for HSIL or cancer</td>
<td>0.5</td>
<td>2.1</td>
</tr>
<tr>
<td>- Percentage of screening tests positive for HSIL</td>
<td>0.5</td>
<td>1.7</td>
</tr>
<tr>
<td>- Percentage of screening tests positive for cancer</td>
<td>0.03</td>
<td>0.3</td>
</tr>
<tr>
<td>Cancer detection rate per 1,000 women screened (final diagnosis)</td>
<td>NA</td>
<td>4.49</td>
</tr>
</tbody>
</table>

NA = not available, HSIL = high-grade squamous intraepithelial neoplasia.
and between primary healthcare units. VIA has also been reported to have an acceptable positive predictive value in populations that are highly affected by cervical disease, which is certainly the case in Cruzeiro do Sul.\(^\text{12-16}\) In the present study, the cervix of the patients was examined using acetic acid and the naked eye, and this increased the number of cervical abnormalities diagnosed by 25.5%. However, this examination should not be named VIA, because this procedure involves a standard routine, i.e. usage of 5% acetic acid and proper personnel training. On the other hand, there is an Atlas dedicated to VIA interpretation.\(^\text{17}\)

## CONCLUSIONS

The results from the present study allow the conclusion that, in the Brazilian Amazon region, it is very likely that the official figures for the incidence and prevalence of cervical disease are underestimated. The large numbers of CIN and cancer cases that were detected might well reflect the ineffective screening in the region, and properly planned and structured public interventions might increase cervical cancer detection rates in such underserved geographical areas. According to data gathered by other authors, VIA might be a highly acceptable option for the screening of cervical abnormalities among the female population in the Amazon region.

## REFERENCES