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Tracking of cervical cancer in 7,519 patients: a study of the prevalence of altered cytologies

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Summary

Purpose: To evaluate the outcome and adherence of 535 patients with cytological changes. *Materials and Methods:* Study of 7519 smear tests harvested in 2007. *Results:* Of the 7,519 (100%) patients analyzed, 6,964 (92.6%) had cytology negative for intraepithelial lesion or malignancy, 535 (7.1%) abnormalities in epithelial cells, and 20 (0.3%) were unsatisfactory. Of these 535 (100%) patients, 511 (95.5%) were referred to the outpatient clinic and colposcopic exam submitted and 24 (4.5%) did not return to the clinic. The group participated in the ambulatory visits, 302 (59.1%) underwent colposcopy-guided biopsy, and the remaining 209 (40.9%) examinations were negative. *Conclusion:* The cytological examination remains the method of choice for cervical cancer screening. It includes low costs, is effective, and well-accepted. Early diagnosis minimises the cost of research. Universities have an important role in the training of health professionals and also in the development of research.

Key words: Uterine cervical neoplasm; Biopsy; Cytopathology; Screening.

Introduction

In the 1940s the tracking of cervical cancer began, following a publication by Papanicolaou and Traut [1] about the cytological coloration technique which allowed the identification of malign neoplasias using a vaginal smear.

Globally, cervical cancer [2, 3] represents a public health problem, with an incidence twice as high in less developed countries, while it is also the third most common form of cancer among women. According to estimates [2, 3] there will be 530,000 new cases of cancer in 2012, and it will be responsible for the death of 275,000 women.

The beginning of sexual activity at a precocious age, the greater number of sexual partners, and multiparity are considered the preponderant risk factors [2] for cervical cancer. There is epidemiological evidence that indicates that it is a sexually transmitted disease (STD) caused by the human papillomavirus (HPV) and is an important risk factor in cervical carcinogensis. Meisels and Morin [4]; Zür Hausen *et al.* [5], and Pater and Pater [6] have confirmed the presence of HPV DNA in the genome of carcinomatous cells. Zür Hausen [7] observed the presence of HPV in more than 90% of squamous cervical carcinomas. In this manner, the relationship between HPV and cervical cancer defined in the above research, as well as in others, can be confirmed.

Epidemiological studies [8, 9] have demonstrated that HPV is responsible for the progression of cervical intraepithelial neoplasias (CIN) with a high level, which can occur up to two years after the primary infection.

Cervical cancer [10] has a long clinical evolution, allowing its detection in an incipient phase. Since the 1960s the practice of tracking has led to a satisfactory reduction in the incidence of mortality in the majority of developed countries.

Papanicolaou's exam is part of this strategy [2] since it has a low cost, is simple to carry out and administrate, can be applied to the whole population, has high sensitivity, and is very specific, as well as allowing the precocious treatment of cancer and its precursory lesions. It is therefore necessary to guarantee the organization, the integrality and the quality of the program, as well as the follow-up of patients.

Stimulated by the Viva Women Program (the National Program for the Control of Cervical and Breast Cancer), created in 1996 in Brazil [11], the control of cervical cancer was consolidated as a priority in the National Policy for Oncological Care (INCA, 2005), in the Pact for Health (Brasil, 2006), and the Plan for Strengthening the Network for the Prevention, Diagnosis, and Treatment of Cancer in 2011. Despite all these government actions, it is the second most frequent tumor [2] in the female population and the fourth cause of death for women due to cancer in Brazil. In 2012, 17,540 cases of cervical cancer are expected [2], with an estimated risk of 17 cases in every 100,000 women and 4,800 fatal victims per year. The initial age group at risk [2] is 20 - 29 years old and the risk increases until it reaches its peak between 50 and 60 years.

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The International Union Against Cancer (UICC) concluded in 2006 [3-12] that in the population tracking there were errors in sampling, in the technique of preparing and processing slides, in the control of laboratory quality, in monitoring, in the interpretation of the smear, and in the preparation and writing of reports. Most responsible for false-negative rates were the precarious collection of samples (60% and interpretation errors 40%).

The importance of cytological tracking in the detection of precursory and invasive lesions has served as a stimulus to evaluate the number of patients with altered cytological exams and lacking outpatient care after the preventive exam.

The main objective of the study was to evaluate the result of 535 cytological changed examinations and specifically, the forwarding and follow-up of patients with altered cytology results and how patients adhere to outpatient control.

Materials and Methods

A transversal study with a retrospective analysis of 7,519 exams of patients who are users of the Sistema Único de Saúde (SUS – Single Health System) in the outpatient clinics of the Department of Gynecology, Escola Paulista de Medicina (EPM) and Universidade Federal de São Paulo (UNIFESP), who during their consultations had material collected for the Papanicolaou exam, in the period between January and December 2007. Included were all patients who were not menstruating and who had not previously done an endovaginal ultrasound, used vaginal cream, and/or had sexual relations in the previous 72 hours.

Cytopathological exam

The exams were carried out by medical residents, post-graduate students, attending doctors, and nursing professionals. The material collected was sent to the Cytopathological Laboratory of the EPM/UNIFESP Department of Gynecology. The collection of the cytopathological exam used the triple technique (collects ectocervica and endocervical, vaginal).

Cytopathological tracking

The cytological readings were interpreted according to the Bethesda System Terminology (BST 2001 - Table 1). Patients with altered cytologies were directed to the Gynecological Diseases Prevention Group (Núcleo de Prevenção de Doenças Ginecológicas – NUPREV) in the Department of Gynecology (EPM/UNIFESP), for diagnostic confirmation using colposcopy exams, biopsies, and anatomopathology exams, and afterwards received the suitable treatment.

Data collection

The results of the cytopathological exams were obtained from the Information System of the Cytopathology Laboratory, Department of Gynecology (EPM/UNIFESP), catalogued in accordance with the entry date of the exam. After this, the development of the patients with abnormalities in epithelial cells was analyzed, with data from January to September 2008 being collected to check anatomo-pathological reports and the scheduling of further outpatient consultations.

Clinical conduct

To analyze the data, the protocol suggested by the National Institute of Cancer (Nacional do Câncer), INCA-2012 [11], was used to follow up the patients who had done the Papanicolaou exam, covering the behavior expected in accordance with the result of the cytopathological exam. Those with references to material that was unsatisfactory for oncological evaluation had to be immediately repeated. Altered cytologies due to low grade intraepithelial lesions (LSIL), epithelial cell abnormalities of undetermined significance (ASC-US), epithelial cell abnormalities cannot exclude - HSIL (ASC-H), and atypical glands had to be treated within, if there was a specific and repeated agent, in a maximum of six months. If cellular alterations persisted, it was important to continue the investigation. In regard to results with high level lesions, epidermoid carcinomas, and invasive adenocarcinomas, investigation with colposcopy and biopsy was indicated.

Table 1. — *Distribution of the cytological results of 535 patients with atypias in epithelial cells. The exams were collected in the Department of Gynecology (EPM–UNIFESP- SP), between January and December 2007.*

Cytological results	No. of cases (%)
Atypias with undetermined significance	173 (32.3%)
LSIL	269 (50.3%)
HSIL	66 (12.3%)
Spinocellular carcinoma	24 (4.5%)
Adenocarcinoma	3 (0.6%)
Total cases	535 (100%)

Ethics committee

This project was submitted to and approved by the Research Ethics Committee of Universidade Federal de São Paulo/Hospital São Paulo.

Results

The research included the tracking of cervical cancer using the Papanicolaou exam in patients between 11 and 89 years of age, with an average age of 45. No patients were excluded after the collection of material.

Of the 7,519 (100%) patients analyzed, 6,964 (92.6%) had negative cytologies for intraepithelial lesions or malignity, 535 (7.1%) had abnormalities in epithelial cells, and 20 (0.3%) of the samples were unsatisfactory. The 20 patients with unsatisfactory exams were recalled twice and 14 continued to have unsatisfactory cytology.

Table 1 shows the results of the cytological exams of the 535 (100%) patients who had abnormalities in epithelial cells. Of this total, 173 (32.3%) had atypical cells with an indeterminate meaning, 269 (50.3%) were LSIL, 66 (12.3%) were HSIL, 24 (4.5%) were spinocellular carcinoma, and three (0.6%) were adenocarcinoma. Also in relation to these 535 (100%), 24 (4.5%) did not return to the outpatient clinic, 511 (95.5%) returned and were directed to the specialized service.

Of the group of 511 (100%) patients who returned, 302 (59.1%) underwent a colposcopy, directed biopsy, and anatomo-pathology, with the treatment carried out according to the biopsy result. For the other 209 (40.9%), the col-

Table 2. — *Cyto-histological correlation of the 76 patients with atypias with an undetermined significance.*

Biopsy result	Cytologies with atypias with an undetermined significance N (%)
Chronic cervicitis	45 (59.2%)
LSIL	27 (35.5%)
HSIL	1 (1.3%)
Spinocellular carcinoma	1 (1.3%)
Adenocarcinoma	2 (2.6%)
Total	76 (100%)

Table 3. — *Cyto-histological correlation of the 226 patients who received LSIL, HSIL, CEC, and adenocarcinoma cytological results.*

	Cytology N (%)			
Biopsy N (%)	LSIL N (%)	HSIL N (%)	CEC N (%)	Adeno-carcinoma N (%)
Chronic cervicitis 58 (25.7%)	50 (22.1%)	8 (3.6%)	0 (0.0%)	0 (0.0%)
LSIL 96 (42.4%)	86 (38.0%)	10 (4.4%)	0 (0.0%)	0 (0.0%)
HSIL 58 (25.7%)	11 (4.9%)	39 (17.3%)	8 (3.6%)	0 (0.0%)
Spinocellular carcinoma 11 (4.9%)	0 (0.0%)	1 (0.4%)	10 (4.4%)	0 (0.0%)
Adenocarcinoma 3 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.3%)
Total 226 (100%)	147 (65%)	58 (25.7%)	18 (8.0%)	3 (1.3%)

poscopy exam was negative and no biopsy carried out, as there was expectant behavior.

Of the 302 (100%) who were biopsied, 76 (25.2%) had atypias with an undetermined significance and the other 226 (74.8%) had intraepithelial lesions of a low or high degree, carcinoma, and adenocarcinoma.

Table 2 shows the cyto-histological correlation of the 76 (100%) patients who had atypias with an undetermined significance. Of this group, 45 (59.2%) received a biopsy result of chronic cervicitis (CC), 27 (35.5%) LSIL, one (1.3%) HSIL, one (1.3%) spinocellular carcinoma, and two (2.6%) adenocarcinoma. Following this, patients who did not have a cyto-histological correlation were investigated.

In Table 3 the cyto-histological correlation of the other patients gave a result of 147 (48.7%) with LSIL, 58 (19.2%) with HSIL, 18 (5.9%) with spinocellular carcinoma, and three (1.0%) with adenocarcinoma. The biopsy was negative for 50 (34.0%) patients who had received a LSIL result from the cytological exam and for (13.8%) with HSIL. These patients were investigated again.

Table 4 shows the 209 patients who had cytological results with an undetermined significance, low and high level

Table 4. — *Result of cytological exam of 209 patients who had a negative colposcopy.*

Cytologies	Colposcopy without biopsy N (%)
Atypias with an undetermined significance	92 (44.0%)
LSIL	105 (50.2%)
HSIL	7 (3.4%)
Spinocellular carcinoma	5 (2.4%)
Total	209 (100%)

Table 5. — *Result of cytological exam of patients with outpatient absenteeism.*

Cytological result	No. of patients in outpatient treatment N (%)
Atypias with an undetermined significance	5 (20.8%)
LSIL	17 (70.8%)
HSIL	1 (4.2%)
Spinocellular carcinoma	1 (4.2%)
Total	24 (100%)

lesions, and carcinomas, who were not biopsied during the colposcopy.

Of the 535 patients with altered cytology, 511 (95.5%) continued treatment in a specialized outpatient clinic. Only 24 (4.5%) did not return to the clinic. Various researches were carried out in the records of these 24 (100%) patients to describe outpatient absenteeism. It was found that 17 (70.8%) used the hospital register (HR) of other patients and seven (29.2%) had not made appointments for socioeconomic reasons.

Table 5 shows the result of the cytological exams of the patients who did not return to the clinic. Of these, the most frequent were the 17 (70.8%%) who had LSIL cytological results, followed by five (20.8%) with atypias with an undetermined significance, one (4.2%) with HSIL, and one (4.2%) with CEC.

Discussion

The high level of prevalence and mortality of cervical cancer [2] found in developing countries causes serious difficulties in public health. Frequent sick leave and hospitalizations prevent patients from exercising their social role in the family and at work. For this reason, educational measures [13], which can explain the natural history of the disease, show the risk factors, and stimulate patient participation in regular exams, are objective attitudes involving the community, with the intention of reducing morbimortality rate.

Medeiros *et al.* [14] observed that among 760,501 women who did the Papanicolaou exam, only 6.4% had altered cytologies. Rama *et al.* [15], in a transversal study with 5,477 women, found that 6.4% of cytologies had ab-

normal results. Corroborating this data, 7,519 patients were tracked and 535 (7.1%) were identified with epithelial cells.

It is a fact that the slow evolution of this cancer allows diagnosis in the intraepithelial phase, in asymptomatic women, where treatment is low cost [16]. In this research Ostor [17] managed to evaluate the regression, persistence, and progression of intraepithelial lesions. He concluded that there was regression in 60% of low grade intraepithelial neoplasia cases, with persistence of 30% and progression in about 10% to high grade intraepithelial neoplasia and 1% to invasive carcinoma. Consequently, delays in tracking can led to progression in the lesion, meaning more invasive treatment is necessary. Hutchinson *et al.*, [18] estimated that around 25% of cases of cervical cancer occur in patients who are regularly examined at least once every three years.

According to the Ministry of Health [19], around 40% of patients who do cytological exams (Papanicolaou) do not return to the clinic to check the result. Often they are the target of tracking. In this study it was found that of the 535 (100%) with altered oncotic cytology, only 24 (4.5%) did not return to the clinic during the period of the research. Tracking of cervical cancer [19] in developed countries improved after criteria were established to control and call patients.

In the study by Thuler *et al.*[20], it was found that of the 10,505,773 exams included in the Cervical Cancer Information System (Sistema de Informação do Câncer do Colo do Útero - SISCOLO) in 2002, 1.66% (144,415 exams) were considered unsatisfactory. These type of exam results cause disturbances for patients and increase the cost of prevention programs. Generally they are mainly associated with problems in the collection and setting of samples. In this study of the 7,519 (100%) patients submitted to cervical cancer tracking, only 20 (0.3%) had unsatisfactory exams.

Triple collection is part of the routine of cervical cancer tracking in the UNIFESP Department of Gynecology. The use of a single slide and triple collection minimizes the cost of the exam, facilitates the reading of slides, as well as increasing the operational capacity of the laboratory, without compromising the final result.

Using SISCOLO, Thuler *et al.* [20] managed to evaluate the monitoring of 1,028 laboratories which carried out Papanicolaou exams and showed the importance of this data for the improvement of cervical cancer tracking programs in Brazil.

Conclusion

Of the 7,519 patients who did a cytological exam, 535 had altered results and were sent to a specialized clinic for further investigations. Out of these 535 (100%) patients, 511 (95.5%) patients were sent to a specialized clinic for a colposcopy, and 24 (4.5%) did not return to the clinic. Finally, of the group who went to the specialized clinic, 302 (59.1%) had a biopsy directed by the colposcopy, while the exam was negative for the other 209 (40.9%). Consequently they had expectant behavior. Patients who did not obtain a cyto-histological correlation were investigated afterwards.

The cytological exam is considered the oldest and best established prevention program. It continues to be the method of choice for tracking cervical cancer. It has a low cost, is efficient, and well-accepted. However, it is a vulnerable to errors in collection and the preparation of slides, and has subjectivity in reading. Precocious diagnosis and treatment minimizes the cost of the entire investigative process. In a general manner, universities have a very important role in the training of specialist doctors, health professions, and also in the preparation of research projects.

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