



## Analysis of the capacity of preventive diagnostic tests for cervical cancer\*

*Análise da capacidade diagnóstica dos exames preventivos do câncer de colo uterino*

*Análisis de la capacidad diagnóstica de los exámenes preventivos del cáncer de cuello uterino*

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### ABSTRACT

**Objective:** To evaluate the diagnostic capacity of cytological, colposcopic, and histological exams on the detection of premalignant lesions. **Methods:** A documentary, retrospective study, with a quantitative approach, conducted in the Cancer Prevention Institute (CPI), in Fortaleza-CE. The population consisted of medical records of 112 women who had the results of these three exams. We adopted the chi-square test and considered it statistically significant when  $p < 0.05$ . We applied sensitivity and specificity, positive predictive value (PPV) and negative predictive value (NPV) for cytology and colposcopy. **Results:** From the comparison between the diagnostic tests, we observed that cytology obtained a sensitivity of 89.8%, a specificity of 35.7%, a PPV of 90.7% and an NPV of 33.3%. Colposcopy achieved a sensitivity of 84.7%, a specificity of 50%, a PPV of 92.2% and an NPV of 31.8%. **Conclusion:** We found that these tests presented sensitivity and specificity that can alternate with one another, indicating the association of both to improve the accuracy of diagnosis of premalignant lesions.

**Keywords:** Women's health; Cervix neoplasms prevention

### RESUMO

**Objetivo:** Avaliar a capacidade diagnóstica dos exames citológicos, colposcópico e histológico na detecção de lesões pré-malignas. **Métodos:** Estudo documental, retrospectivo, com abordagem quantitativa, realizado no Instituto de Prevenção do Câncer (IPC), em Fortaleza-CE. A população foi composta por prontuários de 112 mulheres que possuíam o resultado dos três exames. Adotou-se o teste de qui-quadrado e considerou-se estatisticamente significativo quando  $p < 0,05$ . Foram aplicados a sensibilidade e especificidade, valor preditivo positivo (VPP) e valor preditivo negativo (VPN) para a citologia e colposcopia. **Resultados:** A partir da comparação entre os exames diagnósticos observou-se que a citologia obteve uma sensibilidade de 89,8%, uma especificidade de 35,7%, um VPP de 90,7% e um VPN de 33,3%. A colposcopia alcançou uma sensibilidade de 84,7%, uma especificidade de 50%, um VPP de 92,2% e um VPN de 31,8%. **Conclusão:** Observou-se que esses exames apresentaram valores de sensibilidade e especificidade que podem alternar-se, indicando-se a associação de ambos para melhorar a acurácia do diagnóstico das lesões pré-malignas. **Descritores:** Saúde da mulher; Prevenção de câncer de colo uterino

### RESUMEN

**Objetivo:** Evaluar la capacidad diagnóstica de los exámenes citológicos, colposcópico e histológico en la detección de lesiones pre-malignas. **Métodos:** Estudio documental, retrospectivo, con abordaje cuantitativo, realizado en el Instituto de Prevención del Cáncer (IPC), en Fortaleza-CE. La población estuvo compuesta por historias clínicas de 112 mujeres que poseían el resultado de los tres exámenes. Se adoptó el test de Chi-cuadrado y se consideró estadísticamente significativo cuando  $p < 0,05$ . Fueron aplicados la sensibilidad y especificidad, valor predictivo positivo (VPP) y valor predictivo negativo (VPN) para la citología y colposcopia. **Resultados:** A partir de la comparación entre los exámenes diagnósticos se observó que la citología obtuvo una sensibilidad de 89,8%, una especificidad de 35,7%, un VPP de 90,7% y un VPN de 33,3%. La colposcopia alcanzó una sensibilidad de 84,7%, una especificidad de 50%, un VPP de 92,2% y un VPN de 31,8%. **Conclusión:** Se observó que esos exámenes presentaron valores de sensibilidad y especificidad que pueden alternarse, indicándose la asociación de ambos para perfeccionar el diagnóstico de las lesiones pre-malignas. **Descriptor:** Salud de la mujer; Prevención de cáncer de cuello uterino

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## INTRODUCTION

Cervical cancer (CC) is ranked second as most prevalent cancer in women worldwide. Considering that in developing countries, this cancer is ranked first, and is responsible for thousands of deaths per year<sup>(1)</sup>.

In the last two decades, a reduction in the mortality rates due to this type of cancer was found in countries in Europe and in North America<sup>(2,3)</sup>. However, in developing countries the goals for reducing the number of cases have not yet been attained. In Latin America, although there has been a drop in mortality due to CC, it is still responsible for a significant number of deaths, in spite of the methods of prevention and early detection<sup>(4)</sup>.

In Brazil, the epidemiological diagnosis of the most common diseases have undergone changes over the course of years, and are characterized by the increase in the incidence of malignant neoplasias, such as CC, which is responsible for the death of approximately 230 thousand women per year<sup>(5)</sup>.

There are some predisposing factors for the development of this neoplasia. Among these factors, infection by the Human Papillomavirus (HPV) is outstanding, considering that around 99% of malignant tumors and cervical precursor lesions are caused by one of the 15 oncogenic types of HPV, with types 16 and 18 being the most common<sup>(5)</sup>.

Therefore, in Brazil, the main strategy used for the detection and prevention of CC is the Papanicolaou exam, which consists of the collection and cytological analysis of cervical material, also known as oncotoc cytology, Pap smear, among others<sup>(6)</sup>.

This exam helps with the detection of cellular alterations in the lining of the cervix, before these atypical cells become a cancer. When these alterations are identified, they require complementary exams to enable continuity of the identification of these premalignant lesions<sup>(7)</sup>.

In order to establish a uniform terminology in the diagnosis of CC, the Bethesda system was created in the United States of America in 1988. This system has aggregated the concepts and standardized the nomenclature of cervical smears. In Brazil, this terminology was incorporated into the terms used throughout the services denominated "Sistema Único de Saúde (SUS)" (Brazilian national health system) in 1998, and into those used in the main services that perform cytological exams<sup>(8)</sup>.

From the Bethesda classification, the cervical intraepithelial neoplasias (CIN) are no longer divided into three degrees, and are now divided into Low Grade squamous Intraepithelial Lesions (LGSIL) corresponding to CIN Grade I, and High Grade squamous Intraepithelial Lesions HGSIL, corresponding to CIN Grade II and III and *carcinomain situ*<sup>(9)</sup>.

For many decades, cytology, colposcopy and histology have been the exams considered standard in tracing CC in developed countries, and they are applicable to Brazilian reality, both because of their sensitivity and specificity, and because of their low financial cost, so that all that is required is investment in professional qualification, at all levels in a basic structure that allows wide use of these resources<sup>(10)</sup>.

There is a proven correlation between the results of diagnostic exams for early detection of CC and histopathological exams, and agreement between the methods is observed, therefore this comparison is a way of evaluating the diagnostic capacity of these exams<sup>(11)</sup>. Nevertheless, there is still no certainty about which method is the best to use for tracing this cancer, and indications range from simple cytology through to a DHA=HPV test<sup>(12)</sup>.

Prevention of CC is one of the priority areas of attention in basic care, with the gynecological exam and delivery of the cytopathological results being attributes of the nurse, as a member of the Family Health Strategy team (FHS). From this aspect, it is important for this professional to be alert to the alterations detected in the exam, with the purpose of correctly referring patients, who need to have more invasive procedures performed, to professionals specialized in this area.

The diagnostic criteria of the colposcopic and histopathologic exams have shown to be subjective because of the morphological aspect of each lesion. Therefore, professionals must be judicious, bearing in mind that by not appreciating the presence of minor alterations, this may result in development of the lesion to more advanced stages<sup>(13)</sup>.

In view of the foregoing discourse, the aim of this study was to evaluate the diagnostic accuracy of cytological, colposcopic, and histological exams in the detection of premalignant lesions in women receiving care at a reference center in Fortaleza.

## METHODS

This study, of a quantitative, retrospective nature, was conducted to evaluate the diagnostic test developed at the Cancer Prevention Institute (CPI) ("Instituto de Prevenção do Câncer IPC"), located in the city of Fortaleza – CE. This institution is a reference unit of the service network of the Secretary of Health of Ceara. Patients have access to the unit through centers belonging to the State and Municipality of Fortaleza, where appointments for consultations are made, and care is provided on spontaneous demand, which generates a secondary internal reference.

Data was collected in January 2009, and all the patient charts for the 2 previous years (2007 and 2008),

of women who received care in the gynecology sector were analyzed, with the help of a structured instrument, based on the chart used at the institution. The study population consisted of all the women whose charts contained records of the results of cytological exams showing atypical cells, with colposcopic and histological exams being performed, in a total of 112 women.

The data obtained were stored in the *Excel for Windows* program and analyzed by the *Statistical Package for Social Sciences for Personal Computer (SPSS-PC)*, version 17.0 software, presented in tables and discussed, in accordance with aspects of the pertinent literature.

The Chi-squared test was used with a level of significance of 5%. Sensitivity and specificity, positive predictive value (PPV) and negative predictive value (NPV) were applied for cytology and colposcopy, having histology as the gold standard. Considering that the sensitivity of a test represents the proportion of sick people that the test is capable of detecting. It is calculated by dividing the true positive cases by the sum of these with the false negatives, and multiplying the result by 100. With regard to specificity, it is the proportion non ill people that the test detects, and it is calculated by dividing the number of true negatives by the sum of false positive and true negatives, and multiplying the total by 100<sup>(14)</sup>.

The predictive values are used to predict what the probability would be of having the disease, if the result is positive (PPV), or of not having the disease, if the result is negative (NPV). The PPV is calculated by dividing the true positive results by all the positives and the NPV is calculated based on the division of the truly negative results by all the negative results<sup>(15)</sup>.

The ethical aspects of the research involving human beings were respected, in accordance with those recommended by Resolution No. 196/96. The research project was approved by the Research Ethics Committee of the Federal University of Ceara, in accordance with report number 199/08.

## RESULTS

After data collection, the sample was first characterized. The women's ages ranged from 15 to 80 years, with a mean of 38.3 years (SD=14.1). It was observed that the majority of women had a low educational level, 99 (88.4%), and 63 (56.2%) were married.

As regards gynecological antecedents, 66 (53.6%) presented menarche between 10 and 12 years of age and 52 (46.4%) initiated their sex life between 11 and 15 years of age. Furthermore, 42 (37.5%) had only one sexual partner and 41 (36.6%) did not use contraceptive methods.

These data related to the gynecological antecedents were presented in the data in Table 1.

**Table 1** – Distribution of the women receiving care at the CPI according to the gynecological antecedents. Fortaleza/CE, 2009

| Gynecological Antecedents (n=112)      | n (%)     |
|--|-----------|
| <b>Menarche</b>                        |           |
| 10 to 12 years                         | 60 (53.6) |
| 13 to 15 years                         | 44 (39.3) |
| 16 to 17 years                         | 6 (5.3)   |
| Did not answer                         | 2 (1.8)   |
| <b>Age at beginning of sexual life</b> |           |
| 11 to 15 years                         | 52 (46.4) |
| 16 to 20 years                         | 50 (44.6) |
| 21 to 25 years old                     | 9 (8.1)   |
| Over 25 years                          | 1 (0.9)   |
| <b>Number of Partners</b>              |           |
| 1                                      | 42 (37.5) |
| 2                                      | 31 (27.7) |
| 3                                      | 20 (17.9) |
| 4 or more                              | 16 (14.2) |
| Did not answer                         | 3 (2.7)   |
| <b>Contraceptive Method</b>            |           |
| Do not use                             | 41 (36.6) |
| Tubal ligation                         | 34 (30.4) |
| Male Condom                            | 17 (15.2) |
| Oral Contraceptive                     | 10 (8.9)  |
| Did not answer                         | 8 (7.1)   |
| Injectable                             | 1 (0.9)   |
| IUD                                    | 1 (0.9)   |

After evaluating the characteristics of the population, the results of exams performed were analyzed. In the tables that follow, evaluation of the congruence between cytological and colposcopic exams with the histological exam may be observed. With regard to association between the methods, it is pointed out that the Chi Square test was shown to be statistically significant in the two calculations, with  $p < 0.05$ . The evaluation of agreement between the cytopathological and histological diagnoses may be observed in the data shown in Table 2.

**Table 2** – Comparison between the cytological and histopathological results in the women receiving care at the CPI. Fortaleza-CE, 2009

| Cytology | Histopathology |           | Total       |
|----------|----------------|-----------|-------------|
|          | Present        | Absent    |             |
|          | n (%)          | n (%)     | n (%)       |
| Positive | 88 (78.6)      | 9 (8.0)   | 97 (86.6)   |
| Negative | 10 (8.9)       | 5 (4.5)   | 15 (13.4)   |
| Total    | 98 (87.5)      | 14 (12.5) | 112 (100.0) |

$p=0,009$

In view of the results, it was found that of the 97 (86.6%) women with cellular alteration in the cytological exam, 88 (78.6%) also presented alteration in the histological exam, being truly positive, and 9 (8.0%) were not diagnosed by the second exam, being considered false positives.

Of the 15 (13.4%) women who presented a negative exam for cancer in the cytology, 10 (8.9%) presented a positive result in the histological exam. Therefore, it can be affirmed that the cytological exam was false negative for these 10 (8.9%) women.

Based on these results, the cytological exam presented a sensitivity of 89.8%, specificity of 35.7%, a PPV of 90.7% and PNV of 33.3%.

Agreement between the colposcopy and histology results may be observed in the data shown in Table 3.

**Table 3** – Comparison between the colposcopic and histopathological results in the women receiving care at the CPI. Fortaleza-CE, 2009

| Colposcopia | Histopathology |           | Total       |
|-------------|----------------|-----------|-------------|
|             | Present        | Absent    |             |
|             | No. (%)        | No. (%)   | No. (%)     |
| Positive    | 83 (74.1)      | 7 (6.2)   | 90 (80.3)   |
| Negative    | 15 (13.5)      | 7 (6.2)   | 22 (19.7)   |
| Total       | 98 (87.6)      | 14 (12.4) | 112 (100.0) |

$p=0,009$

It was observed that among the 90 (80.3%) positive colposcopic results, 83 (74.1%) were confirmed by the histological exam and seven (6.2%) were discarded. Of the negative colposcopy results which, however, were sent for histological exam due to clinical indication, 15 (13.5%) were diagnosed as lesions present, and these were considered false negatives; and seven (6.2%) presented absence of lesions, being truly negative.

In view of the above results, the sensitivity of colposcopy was 84.7%, specificity 50%, the PPV 92.2% and PNV 31.8%.

## DISCUSSION

Cancer of the cervix (CC) is preceded by intraepithelial alterations that progress slowly, and may take from 10 to 20 years to become invasive<sup>(2)</sup>. This fact leads one to emphasize that the age-range for performing preventive exams plays a fundamental role in the detection of precancerous lesions, and therefore, in the progression to CC.

A study that analyzed 88,044 hospitalizations with diagnosis of cancer of the cervix, between the years 2002 and 2004, identified the age-range with the highest prevalence was between 20 and 44 years<sup>(16)</sup>, corroborating the mean age of this study, which was 38.3 years.

In addition to this, the age, educational level and marital status are considered risk factors for the acquisition of CC, and for not undergoing this exam for the prevention of this disease. In the present study, the majority of the women were young adults, with a low educational level, and married, corroborating studies that point out these factors as predisposing to the difficulty of diagnosing cervical lesions due to non appearance at the health services<sup>(17)</sup>.

The identification of the risk factors prevalent in women may provide important information for molding the services of triage in developing countries, to adopt strategies for capturing them<sup>(18)</sup>. Knowing the risk factors, the health professional is able to provide counseling and guidance for the practice of self-care with greater efficacy.

The data with reference to the gynecological antecedents showed that the majority of women had early menarche and coitarche, with the two events frequently coinciding with the age at the time of occurrence, in addition to the reduced use of contraceptives, which represents a risk to the sexual and reproductive health of these women, since they are more susceptible to the acquisition of Sexually Transmittable Diseases (STD)/HIV/aids due to the immaturity of the reproductive system<sup>(19)</sup>.

A study conducted with 433 women submitted to cytological exam and HPV diagnosis, showed a statistically significant relationship between the early age of coitarche and greater prevalence of HPV<sup>(20)</sup>.

It is pointed out that there have been an increasing number of women in relationships of fixed partnership acquiring STD, because of the non use of preservatives or sporadic use in extra-conjugal relationships. This was shown in a study conducted with 5,981 persons in Minas Gerais, in which 60.4% of the men and only 42.7% of the women mentioned the conscientious use of preservatives. When questioned with respect to fixed partnership, 58.4% of the men and 43.5% of the women said they did not use preservatives because they trusted their partners<sup>(21)</sup>.

This vulnerability may predispose to the acquisition of sexual diseases, which lead to gynecological alterations, and must be diagnosed early by exams available in the health services.

With regard to these exams, based on this study it may be inferred that although the majority of patients affected by CC were detected by means of the cytological exam, a large number of women were not diagnosed in an effective manner, which will result in discontinuity in having the more specific exams performed, if only the cytological result were considered.

In spite of the cytological exam being the first choice for tracing CC, it has a high proportion of false positive results that range from 2% to 62%<sup>(13)</sup>.

In addition to this, a low specificity leads to a higher rate of false positive results; that is to say, healthy women

were diagnosed falsely as being ill. The erroneous result of this test involves in the continuity of invasive exams, unnecessarily, raising the costs of the health services, in addition to causing the client emotional damage.

Corroborating the findings of this study, a research conducted with 100 patients in a cervical pathology ambulatory clinic, found a high sensitivity and low specificity for the cytological exam, 96.2% and 69.3%, respectively, with these percentages being influenced by the time when the exam is performed, quality of collection and by the cytology readout<sup>(11)</sup>.

In a review performed in the MEDLINE database with respect to the effectiveness of cytology, 88 studies about the subject were found. In these, the sensitivity of the exam ranged between 48% and 83% and the specificity was between 84% and 97%<sup>(22)</sup>. Thus, this variation was associated with the subjectivity of the professional who performed the exam and to the interpretation of the observer when analyzing the slide<sup>(23)</sup>.

The predictive values depend on, among other factors, the prevalence of the disease in the population being evaluated<sup>(11)</sup>. It is important to point out that in order to affirm the PPV of cytology with greater precision, further studies must be conducted, preferably using a sample with an equal number of positive and negative cases.

Furthermore, the high index of cases of CC, which were diagnosed with the histological exam, is pointed out, and which were not diagnosed with the cytological exam, showing that women who were ill could have been treated adequately right from the beginning, and that this treatment was retarded by the absence of diagnosis.

In order to obtain high sensitivity, it is necessary for the procedure to be adequately performed at all stages, starting right from the appropriate guidance of clients, through to the interpretation of slides. From this aspect, the nurse is one of the professionals who is most able to intervene in this process, as he/she works directly with the clientele, and can provide general information that precedes the exam and that may help it to be performed in a better manner.

When the whole of this process is not satisfactory, complementary results from cytology and histology may be found to elucidate the result. Colposcopy has assumed an intermediate role between cytology and histology, functioning as a method of tracing cervical pathology<sup>(24)</sup>. In view of this statement, one has colposcopy as a choice after an altered result obtained by the cytology exam.

The Ministry of Health affirms that colposcopy presents high sensitivity and low specificity, which makes it unfavorable as the first choice for the diagnostic method for CC, since it provides a high rate of over-diagnosis and overtreatment of women<sup>(6)</sup>.

In this study, colposcopy was shown to be more specific than cytology, corroborating a study conducted

with 100 women in João Pessoa, between August 2006 and August 2007, in which colposcopy presented a specificity of 78.7% and cytology, 69.3%<sup>(11)</sup>.

A study conducted with 397 women in Pernambuco, who had undergone exams for tracing CC, observed a weak agreement between colposcopy and histopathology, because in 77.5% of the cases, colposcopy did not improve the diagnosis of intraepithelial neoplasias. Moreover, in 22.5% of the cases, although colposcopy had presented abnormal findings, histopathology did not reveal any abnormalities, suggesting a weak agreement of the satisfactory colposcopies. Therefore, it is suggested that the value of colposcopy served, above all, to locate the best site for proceeding with the biopsy, and not to increase the diagnostic accuracy of cervical intraepithelial lesions<sup>(12)</sup>.

It is known that a highly sensitive and not highly specific exam must be the choice in a program for tracing CC, with the purpose of detecting all the positive cases of cervical lesions, although some healthy women were diagnosed erroneously as having disease<sup>(11)</sup>.

In the present study, analysis of the results of the three exams demonstrated variability in their sensitivity and specificity. Therefore, there is a need for making these exams available in an ample manner and accessible to the entire population, so that cervical lesions may be rapidly detected, and their progression followed up.

## CONCLUSION

This study showed that cytology was more sensitive than colposcopy, and this was more specific than cytology, when compared with histology, considered the gold standard for the comparisons made. Therefore, the result of this research points out the possibility of associating the two exams, as methods for tracing cervical cancer, and may substantially improve the diagnostic accuracy of premalignant lesions of the cervix.

Therefore, it is essential for professionals involved in the diagnosis of this pathology work in agreement, in order to guarantee the maximum quality and accuracy of the exams.

In view of the foregoing discussion, nursing professionals may become important agents, as they represent the main articulators of the health-disease process in the population submitted to gynecological consultations, both as regards the performance of exams and in referring patients to reference services during the consultation of nursing in gynecology, with the purpose of having more complex exams performed.

One therefore perceives the importance of conducting studies that enable the periodic evaluation of the specificity and sensitivity of routine exams for the prevention of CC, in order to characterize their quality, and identify possible interfering factors in the reports.

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