









Limitation of cytology and the impact on reduction of cervical cancer

Limitação da citologia e o impacto na redução do câncer de colo uterino

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ABSTRACT

Introduction: Cervical cancer is the third most common malignant tumor in the female population and the fourth cause of death from cancer in women in Brazil. The squamocolumnar junction and the transformation zone concentrate 90% of pre-invasive and invasive cervical lesions. **Objective:** To evaluate the prevalence of cytology without cells of the squamocolumnar junction and feasibility of active search. **Methods:** Cross-sectional study at a university hospital between 2017 and 2018. The prevalence of cytology without squamocolumnar junction cells was calculated. A convenience sample was obtained and mean age and relationship with presence of transformation zone cells were calculated. An active search was performed and cytology collected, with estrogen preparation if indicated. Medical records of the other women were analyzed. **Results:** Squamocolumnar junction cells were not found in 28.84% of samples. Mean age was 53 years, without association with presence of squamocolumnar junction cells ($p=0.409$). Seventy-six women returned, 36 of which (47.37%) used estrogen. Level 2 or 3 cervical intraepithelial neoplasia, microinvasive carcinoma or cancer was not identified. A total of 134 medical records were analyzed; only 36 women (26.87%) completed screening. **Conclusions:** The presence of squamocolumnar junction cells indicates quality of cytology; the use of estrogen in postmenopausal women favors its collection. There were difficulties in active search. An immediate repetition of cytology should be considered.

Keywords: Papanicolaou test; papillomavirus infections; cervical intraepithelial neoplasia; prevalence.

RESUMO

Introdução: O câncer de colo uterino é o terceiro tumor maligno mais frequente na população feminina e a quarta causa de morte de mulheres por câncer no Brasil. A junção escamo-colunar e a zona de transformação concentram 90% das lesões pré-invasoras e invasoras cervicais. **Objetivo:** Avaliar prevalência de colpocitologias sem células da junção escamo-colunar e a viabilidade de busca ativa. **Métodos:** Estudo transversal em hospital universitário entre 2017 e 2018. Calculada prevalência de citologias sem células da junção escamo-colunar. Obtida amostra por conveniência, calculada média de idade e relação com a presença da junção escamo-colunar. Realizada busca ativa e colhidas citologias com preparo estrogênico, se indicado. Analisados os prontuários das demais mulheres. **Resultados:** A prevalência de ausência de células da junção escamo-colunar foi de 28,84%. A média de idade foi 53 anos, sem associação com presença da junção escamo-colunar ($p=0,409$). Retornaram 76 mulheres e 36 (47,37%) usaram estrogênio. Não identificamos neoplasia intraepitelia cervical graus 2 ou 3, carcinoma microinvasor e câncer. Analisados 134 prontuários, dos quais apenas 36 mulheres (26,87%) concluíram o rastreamento. **Conclusões:** A presença de células da junção escamo-colunar indica qualidade da coleta, e o uso de estrogênio na pós-menopausa favorece sua obtenção. Houve dificuldade de busca ativa. A repetição imediata da citologia deve ser considerada.

Palavras-chave: Teste de Papanicolaou; infecções por papillomavirus; neoplasia intraepitelia cervical; prevalência.

INTRODUCTION

According to data from Brazil's National Cancer Institute (INCA), when non-melanoma skin cancer is excluded, cervical cancer becomes the third most common malignant tumor in the female population, behind only breast cancer and colorectal cancer, with an estimated 16,710 new cases in Brazil in 2020. It is the fourth leading cause of death in women from cancer in Brazil, where it accounted for 6,526 deaths in 2018⁽¹⁾.

In Brazil, cervical cancer screening is carried out with the Pap smear, in an opportunistic way; that is, women seek health services for some reason and the physician takes the opportunity to obtain a sample of cervical material. However, as it is not an organized screening, achieving adequate population coverage within the scope of primary care to obtain a significant reduction in the incidence of cervical cancer and associated mortality remains a challenge^(2,3).

A limitation of the Pap smear is its low sensitivity, ranging from 50 to 60%; therefore, repetition is necessary to ensure a greater degree of sensitivity. The specificity of the test is high, since the proportion of women without disease with a negative test is high⁽⁴⁾.

The squamocolumnar junction (SCJ) and the transformation zone (area that corresponds to the metaplastic epithelium located between the glandular and the original squamous epithelium) concentrate about 90% of precursor or malignant lesions of the uterine cervix⁽⁵⁾. The presence of cells from the SCJ/transformation zone is not necessary for the sample to be satisfactory; however, it has been considered an indicator of the quality of the cytological sample⁽⁶⁾.

The clinical significance of cervical cancer screening in the absence of SCJ cell representation is still controversial. Studies have not shown an increase in the incidence of cervical intraepithelial neoplasia and cervical cancer in these patients⁽⁷⁾. However, according to Aghajani and coworkers (2006), 56% of false-negative cases in the Pap smear are due to the absence of sufficient endocervical cells, which would lead to later diagnoses and increased morbidity and mortality rates⁽⁸⁾.

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Knowledge of the prevalence of Pap smear tests that show only squamous epithelium cells in health services is important so that their causes may be investigated and corrected.

We know that in research, teaching and training hospitals, such as university hospitals, the professionals involved in the care of the population have different levels of experience. Thus, we could investigate whether sample collection in Pap smear examinations performed by medical students working in the gynecology service of these hospitals could contribute to a higher incidence of cervical cytology examinations with unrepresented SCJ.

The Brazilian Guidelines for the Screening of Cervical Cancer and international protocols recommend that normal smears without the presence of any SCJ component be repeated within one year, and with two consecutive normal and complete annual examinations, the interval will then be triennial^(9,10).

Despite advances in the Unified Health System (SUS) and actions aimed at encouraging the prevention of cervical cancer, INCA's current statistics confirm that this objective remains a challenge.

OBJECTIVE

To assess the prevalence of Pap smear reports without SCJ and CIN 2+ (cervical intraepithelial neoplasia grades 2 or 3, microinvasive carcinoma or cancer) in women treated at a university hospital and to analyze the feasibility of actively seeking these women for adequate cervical cancer screening.

METHODS

We carried out a cross-sectional study at the Gynecology Service of the Antônio Pedro University Hospital (HUAP), of the Fluminense Federal University (UFF), Niterói, Rio de Janeiro, on the basis of records of the HUAP Pathology Service between the years 2017 and 2018; we determined the prevalence of cytology without representativeness of SCJ cells after excluding examinations of hysterectomized women.

From this total number of exams, those who showed any degree of atypia in squamous cells or who came from women who had previously undergone diagnostic or therapeutic procedures in the uterine cervix were excluded. A convenience sample was obtained from the Pap smears that were available for evaluation by the researcher at the gynecology outpatient clinic. The mean age of the women was calculated and a logistic regression analysis was performed to identify and quantify the effect of age on the presence of SCJ components.

An active search for these women was then carried out by telephone, through landline and/or cell phone registered in the HUAP registration system. In those successfully contacted, two new cytology tests were obtained, at six and 12 months, to identify SCJ cells and the existence of CIN 2+, with calculation of prevalence in both samples.

The examinations were performed on two slides, with the aim of increasing their sensitivity. For postmenopausal women, estrogen preparation was performed prior to cytology collection, using promestriene vaginally for 21 days, with interruption two days before collection.

In the group of women in which telephone contact was not possible, an analysis of the medical records was performed to assess whether they had completed the appropriate screening and to verify the occurrence of CIN 2+.

This project was submitted to and approved by the HUAP Research Ethics Committee Involving Human Beings (Opinion 2,763,774). Women aged 25 years or older were included in the study after signing an informed consent form.

RESULTS

A total of 2,895 Pap smears were performed at HUAP in 2017 and 2018, with 1,483 tests performed in 2017 and 1,412 in 2018. Of the total number of tests performed, 835 did not have representative SCJ cells, with a prevalence of 28.84%.

After applying the exclusion criteria, it was observed that of the 835 women with tests without representativeness of SCJ cells, 724 could be part of the present study.

A total of 210 women were selected through a convenience sample. The mean age was 53 years (25 to 77). There was no statistically significant association between age and the presence of SCJ cells in Pap smears ($p=0.409$).

After trying to contact the 210 women by telephone, in 76 (36.19%) we were successful, and four of them (5.26%) had cytological alterations in the Pap smears performed. One woman presented with atypical glandular cells of undetermined significance (AGC) at 12 months and was referred for colposcopy at the Cervical Pathology Outpatient Clinic. After adequate investigation, this patient underwent total abdominal hysterectomy, indicated by uterine myomatosis and abnormal uterine bleeding, with a histopathological report of STUMP (smooth uterine muscle of uncertain malignant potential) surgical specimen, which corresponds to a uterine muscle tumor, smooth with undetermined malignant potential, and mild cervicitis. One woman had both cytological examinations with a low-grade squamous intraepithelial lesion (LSIL), at six and 12 months, and was also referred for colposcopy. A woman with human immunodeficiency virus (HIV) presented with atypical squamous cells of undetermined significance (ASC-US), in the examination performed at six months, being immediately referred for colposcopy. Finally, one woman had an ASC-US result in the collection performed at 12 months and was later submitted to a repeat examination.

It should be noted that, of these 76 women, 36 (47.37%) were subjected to estrogen preparation prior to Pap smears, and in 29 cases (80.56%), it was possible to identify SCJ cells in the Pap smear after preparation. In only seven women (19.44%) was there a continued absence of SCJ components.

No woman had a Pap smear test suggestive of a high-grade squamous intraepithelial lesion (HSIL). Thus, the prevalence of CIN 2+ in women in this group was 0% at six and 12 months after cytology without representation of SCJ cells.

The analysis of the medical records of the 134 women (63.81%) with whom contact was not possible showed that 94 (70.15%) of them did not adequately complete the screening for cervical cancer; 43 (32.09%) did not return to the clinic and 51 (38.06%) did not undergo a new examination, despite returning. In the 36 (26.87%) who had repeated cytology, the test was normal. Finally, four

women (2.99%) underwent total hysterectomy for benign pathology and the histopathological reports of the surgical specimens did not show any cervical lesion.

For women in this group, both those submitted to the new sampling and those who had the anatomopathological reports of the surgical specimens evaluated, the prevalence of CIN 2+ was 0%.

DISCUSSION

The Pap smear was introduced as a screening test in most countries during the 1960s, and, in the 1970s, it was responsible for the reduction in the incidence of cervical cancer in the world⁽¹¹⁾.

An adequate SCJ sample requires the presence of at least 10 well-preserved endocervical or metaplastic cells. Approximately 10 to 20% of cytological samples lack a SCJ component, mainly in postmenopausal women⁽⁶⁾. The lack of representativeness of SCJ cells is an important limiting factor in the quality of Pap smear tests for the adequate screening of cervical cancer and precursor lesions⁽⁸⁾.

We must consider that as the proportion of adenocarcinomas is increasing and that they usually arise in the glandular cells of the endocervix, so it is plausible that the detection of such cancers is reduced in samples that do not have any component of the SCJ; however, there is still little data to support or refute this concern⁽¹²⁾. It has been demonstrated that the SCJ and the transformation zone concentrate 90% of precursor lesions and cervical cancer⁽⁵⁾, and that their location varies according to the age and hormonal status of the woman⁽¹³⁾.

Meta-analyses showed that the sensitivity of the Pap smear is approximately 58%, and that most false-negatives are due to inadequate collection^(14,15).

The prevalence of cytology tests without representation of SCJ components found in the present study (28.84%) was consistent with literature data, even though they were performed in a university hospital.

In a study carried out at the University of Santa Cruz do Sul (UNISC) about cytopathological changes in Pap smears in the city of Santa Cruz do Sul, Rio Grande do Sul, Brazil, the reports showed that 28.6% of the collections had only the squamous epithelium, 63.2% squamous and glandular epithelium, 6 squamous, glandular and metaplastic epithelium, 2.1% squamous and metaplastic epithelium and 0.1% only glandular epithelium. The article warned that the absence of one of the epithelia does not guarantee the absence of neoplastic or precursor lesions, raising the possibility of false-negative results due to an inadequate sample⁽¹⁶⁾.

A compatible result was also obtained in a study carried out at the Federal University of Ceará, in which 194 medical records of women treated at a primary care unit were analyzed, and it was observed that 72.2% of the cytopathological tests were considered satisfactory; however, 25.8% of these were limited by the absence of endocervical cells⁽¹⁷⁾.

Longatto Filho et al. (2002) analyzed 10,438 reports and compared the numbers of positive cases in groups of samples with different quality standards: satisfactory and satisfactory but with some limiting factor, such as absence of SCJ cells, desiccation, purulent background, etc. They concluded that there was a need for adequate sampling, especially with the representativeness of SCJ cells, since

the percentage of positive cases (atypia of undetermined significance, cervical intraepithelial neoplasia (CIN) grades 1 to 3 and carcinoma) was higher in the group of samples considered satisfactory than those that presented some limitation (3.28% in one health unit studied and 5.25% in the other)⁽¹⁸⁾.

Amaral et al.⁽¹⁹⁾ analyzed 10,951 results of cervical cytopathological examinations performed at the SUS in Goiânia between 2004 and 2005 and found that 5,104 smears, despite being satisfactory, had factors that could compromise the analysis, the most frequent being the lack of representation of SCJ components, which occurred in 2,672 tests. The study demonstrated a significant association between altered results and the presence of endocervical cells. The frequency of more severe lesions, such as high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells cannot exclude high grade lesion (ASC-H), and AGC was three to four times higher when there was no limiting factor, such as the absence of endocervical or metaplastic cells⁽¹⁹⁾.

The literature lacks studies that assess the quality of the Pap smear collection performed by graduating medical students. In searching Brazilian databases, we found no studies involving medical students in university hospitals.

A study carried out in Sorocaba/São Paulo compared smears collected by third-year nursing students, in the curricular internship, under the supervision of the professor of the discipline, with smears performed by professionals, in the same health units, in the same period of time. The study found that 37.5% of examinations performed by professionals on women aged 40 years or older were considered unsatisfactory, versus 5.6% of examinations performed by students, and that the predominant cause of dissatisfaction, for both groups, was absence of SCJ cells⁽²⁰⁾.

The location of the SCJ varies with age and hormonal status. Under the influence of estrogen, for example, in adolescence, during pregnancy and with the use of combined hormonal contraceptives, the SCJ can undergo eversion to the ectocervix; while in situations where there is low estrogen, such as menopause and prolonged lactation, it tends to enter the cervical canal⁽²¹⁾. Thus, age is one of the factors that can influence the presence of SCJ cells in a Pap smear result.

A retrospective study carried out at the Pathological Anatomy Laboratory of the University of Western Sao Paulo (UNOESTE) reviewed 21,866 Pap smear reports and found that the age of the patients influenced the representativeness of SCJ cells in the examinations. Of the patients included, 81.5% were under 40 years of age, and of these, only 11.2% did not have SCJ material in their smears, while 47% of patients aged 40 years and over did not. In addition, in patients aged 40 years and over, the presence of SCJ material progressively decreased with advancing age, occurring mainly in patients over 60 years of age⁽²²⁾.

The mean age of the women whose Pap smear results did not show representativeness of SCJ cells and were selected for the present study was 53 years. Although no statistically significant association was observed between age and the presence of SCJ cells in Pap smears ($p=0.409$), performing estrogen preparation in postmenopausal women — in accordance with the current recommendations of the Brazilian Screening Guidelines of Cervical Cancer, from the Ministry of Health (MS)⁽⁹⁾ — favored obtaining SCJ cells in the cytological results. In our study, a total of 36 women (47.37%)

were subjected to estrogen priming prior to Pap smear collection, and SCJ cells were identified in the results of 29 (80.56%) of them.

The current MS Guidelines⁽⁹⁾, as well as international protocols⁽¹⁰⁾, recommend that Pap smear tests without SCJ representation be repeated in one year. However, we found that success in contacting 210 women for repeat Pap smear testing after results showing the absence of SCJ components was obtained in only 36.19% of cases (76 women), despite the fact that the study was carried out in a university hospital. This difficulty stemmed from the fact that the telephone contacts of the patients were outdated in the HUAP patient identification system.

Of the 134 women from whom the information was obtained through the analysis of medical records, 94 (70.15%) did not have adequate screening for cervical cancer and its precursor lesions, since they did not undergo a new collection 12 months after inadequate Pap smear, even though they were treated at a university hospital. Of these women, 43 (32.09%) never returned to the HUAP Gynecology Outpatient Clinic and 51 (38.06%), despite having returned for a clinical visit, were not submitted to a new cytological collection.

Based on this observation and the knowledge that screening in our country is not organized, the non-repetition of unsatisfactory tests could represent the loss of follow-up of a woman without adequate screening.

The sample size of our study was insufficient to carry out statistical analyses that could suggest a reduction in the collection interval in case of a result without representativeness of SCJ cells, currently recommended at 12 months by the Brazilian Guidelines for the Screening of Cervical Cancer⁽⁹⁾.

However, we can assume that the difficulty in the active search for women, as found in our study, may be a factor that makes it difficult to adequately screen for cervical cancer and its precursor lesions. Accordingly, every effort should be made so that the collection of the Pap smear test is performed under conditions that allow obtaining SCJ cells, avoiding its performance in women who present inflammatory processes and genital bleeding, as well as menopausal women without previous preparation with estrogen. Repeating cytology at the time the patient receives the test result without representativeness of SCJ cells could be a strategy to be considered, given the difficulty in contacting them later.

Strengths: The present study found a prevalence of Pap smear samples without SCJ representation, similarly to the literature. A study that points out the difficulty of actively seeking women for adequate screening for cervical cancer allows the creation of strategies that favor this screening.

Limitation: The sample size of the present study made it impossible to carry out statistical analyses that could suggest a reduction in the collection interval in case of cytology without SCJ representation. Outdated information in the hospital registry made it difficult to actively search for patients.

CONCLUSION

We conclude that the prevalence of missing SCJ components in the Pap smear performed in a university hospital was similar to that of non-university hospitals. The non-identification of CIN 2+ in the cytological follow-up suggests that the repetition of a Pap smear test

in 12 months, recommended by the current Guidelines⁽⁹⁾, seems to be effective. However, the women's difficulty in actively achieving this jeopardizes this screening. Thus, the Pap smear should be performed under conditions that allow, as much as possible, obtaining SCJ cells, such as estrogen priming in menopause. Repeat cytology at the time of receiving the test result is a strategy to be considered.

Approval by the Human Research Ethics Committee

The present study was approved by the Committee of Ethics in Research Involving Humans of Hospital Universitário Antônio Pedro (Approval 2.763.774).

Participation of each author

DSAM: conceptualization, data curation, formal analysis and writing – original draft. ICCVG: conceptualization, supervision and writing – review & editing. SCAVF: conceptualization, supervision and writing – review & editing. CAOM: conceptualization, formal analysis and writing – review & editing. LGCV: formal analysis. PLC: data curation. ICST: data curation. JSSM: data curation.

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Conflict of interest

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