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Fatores associados às alterações cérvico-uterinas de mulheres atendidas em um município polo do oeste catarinense

Factors associated to uterine-cervix changes in women assisted in a pole town in western Santa Catarina

Factores asociados a anomalías cérvico-uterinas en mujeres asistidas en una ciudad polo en el oeste de Santa Catarina

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ABSTRACT

Objective: To identify the cervical-uterine abnormalities in cervical screening and associated factors. **Methods:** A retrospective study conducted by analysis of cervical screening recorded in the Cancer Information System, in the South of the country, in 2014. The final sample included 1.157 reports. For data analysis the SSPP software was used. The study was approved by the Research Ethics Committee on human subjects at the Federal University of Southern Frontier under CAAE nº 46421815.0.0000.5564. **Results:** Predominated in the samples lactobacilli as microbiological agents and Gardnerella vaginalis as infectious agent. changed cervix, presence of metaplastic cells associated with the diagnosis of metaplasia was prevalent in women 25-34 years. Inflammation (18.9%), followed by cytological findings (11.8%), were the most frequent changes. **Conclusion:** The age of 25 to 64 years old, use of the contraceptive pill, Hormonal Replacement Therapy and metaplastic epithelium were associated with the risk of cellular changes occurring.

Descriptors: Papanicolau test, Screening programs, Sexual and reproductive health.

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RESUMO

Objetivo: Identificar as alterações cérvico-uterinas nos exames citopatológicos e seus fatores associados. **Métodos:** Estudo retrospectivo realizado pela análises dos exames citopatológicos registrados no Sistema de Informação do Câncer no sul do país em 2014. A amostra final resultou em 1.157 laudos. Para a análise dos dados foi utilizado o *software* SSPP. O estudo foi aprovado pelo Comitê de Ética e Pesquisa com seres humanos da Universidade Federal da Fronteira Sul sob CAAE nº 46421815.0.0000.5564. **Resultados:** Predominou nas amostras os *lactobacilos* como agentes microbiológicos e a *Gardnerella vaginalis* como agente infeccioso. O colo uterino alterado, a presença de células metaplásicas associado ao diagnóstico de metaplasia foi prevalente nas mulheres de 25 a 34 anos. As inflamações (18,9%), seguido dos achados citológicos (11,8%), foram as alterações mais frequentes. **Conclusão:** Associaram-se ao risco de ocorrência das alterações celulares idade entre 25 a 64 anos, uso da pílula anticoncepcional, Terapia de Reposição Hormonal e epitélio metaplásico.

Descritores: Teste de papanicolau, Programas de rastreamento, Saúde sexual e reprodutiva.

RESUMEN

Objetivo: Identificar las anomalías cérvico-uterinos en el cribado cervical y factores asociados. **Métodos:** Estudio retrospectivo realizado mediante el análisis de cribado cervical registrado en el Sistema de Información sobre el Cáncer en el Sur en 2014. La muestra final incluyó 1.157 informes. Para el software de análisis de datos se utilizó SSPP. El estudio fue aprobado por el Comité Ético de Investigación en seres humanos de la Universidad Federal del Sur de la Frontera bajo CAAE nº 46421815.0.0000.5564. **Resultados:** Predominaron en las muestras de *lactobacilos* como agentes microbiológicos y *Gardnerella vaginalis* como agente infeccioso. El cuello del útero cambiado, la presencia de células de metaplasia asociados con el diagnóstico de metaplasia era frecuente en las mujeres de 25-34 años. Inflamación (18,9%), seguido por los hallazgos citológicos (11,8%) fueron los cambios más frecuentes. **Conclusión:** Se asocian con el riesgo de que se produzcan cambios en las células entre 25 años a 64 años, el uso de píldoras anticonceptivas, la terapia de reemplazo hormonal y el epitélio metaplásico. **Descriptores:** Prueba de papanicolau, Programas de seguimiento, Salud sexual y reproductiva.

INTRODUCTION

The changes found in the cervix region of women's uterus is an inflammation and/or injury caused by a set of reactions to any tissue aggression, bacterial, viral, fungal, parasitic or post-traumatic, that can lead the woman to a health condition that precedes cervical cancer or even worse, the cancer itself.¹ These injuries are, most of the time, asymptomatic, and can be detected through the periodic performance of the preventive cytopathology smear, or Pap smear. Considered an efficient tool to screen Cervical Cancer (CC), it is a cheap, fast and painless method that can be performed in the first level of healthcare.² This cytology was developed for the identification, in the microscope, from epithelial cells, of the agents that cause the development of cervical cancer over 50 years ago, even if the characteristic symptoms are not present.³

Although Brazil was one of the pioneer countries to use this method in public healthcare services, cervical cancer is still the third greatest cause of female cancer and the fourth cause of death by cancer in the country.⁴ It is estimated that, in the world, 529.512 new cases of cervical cancer are found per year, and that it is responsible for the death of approximately 275 thousand women.⁵ In spite of the wide coverage for women assisted in the primary healthcare scope and the facility to access the healthcare services, the test coverage proportion in the country is 77,49% of women from 25 to 64 years old, below the national and international directives that establish a coverage of 80% to achieve the epidemiologic impact in the reduction of this disease rates.⁶⁻⁷

Among the risk factors determinant to the occurrence of cervical cancer, the Human Papillomavirus (HPV) infection seems to have the greatest impact, followed by low immunity, genetics, sexual behavior, age over 30 years and tobacco use.⁸ Thus, this assumes that the cellular changes that precede the highly oncogenic lesions may have their origin in the demographic and behavioral determinants, as well as in the characteristics of each woman. The population diversity of the women assisted in the public healthcare services results in the need to identify possible improvement factors in the programs oriented to this population, at establishing a service able to fulfill the actual needs of these women.⁹

The assessment of the women's healthcare policy in the primary level in Brazilian cities showed technical and management difficulties in most of them, resulting in questions about the quality of the service provided to women and the impact of the healthcare results indicators in this group.¹⁰ In this perspective, some studies assessed the cytopathology reports, tracing the profile of the microorganisms found and the degree of inflammation in the cervical cells. However, studies that assess the cellular changes and the factors associated to their occurrence are still in their early stages.^{5,11}

Considering that the nursing gynecological consultation and the test collection are actions exclusive of the nurses, in the nursing team, upon knowing the factors associated to the occurrence of cervical lesions, the possibility to subsidize the conduction and adoption of therapeutic protocols that are efficient to control the incidence of cervical malignant and precursory lesions, impacting the women's reproductive health. Considering this, our objective was to identify the cervical changes in the cytopathology tests collected from women and the factors associated to their occurrence in a city with regional significance in the west of the state of Santa Catarina.

METHODS

This is a descriptive, retrospective and quantitative study conducted from the analysis of cytopathology exam reports registered in the Cancer Information System (SISCAN) in the city of Chapecó. Located in the West region of the state of

Santa Catarina, the city has 626.057 Km² territorial extension and an estimated population of 205.795 inhabitants, of which 92.904 are women.¹² The municipality under study exercises the function of Old West Capital, considered the main city in the region and reference for healthcare services in approximately 200 towns (equivalent to 1 million people).¹³

To determine the sample calculation, the total population tested in the previous year to the collection of data recorded in the city's SISCAN was considered. From the 19.296 tests, and to ensure a greater statistical confidence, 3% of estimate error and 97% confidence were added for the definition of the sample. Considering the proportional stratification and representative of the population of tests in each healthcare facility, we defined the number of tests that were assessed in each facility. Thus, after the sample calculation, the number of reports accessed in the city was 1.157, evenly distributed in the city's 29 healthcare facilities.

The reports selection was performed through the ordinal sequence in which they were shown in the system, starting from the first report and successively until the total number of tests in each facility was reached. Thus, the inclusion criteria were: the reports registered in SISCAN and released to the patients in 2014. To ensure the confidentiality of the data collected, the anonymity was ensured for the research reports, and each was identified by a code started with the letter "L", from "report" (laudo, in Portuguese), followed by the Arabic number regarding the collection order (L1, L2, L3...). The patients' names were not mentioned.

Data were collected by a semi-structured instrument, built by the researchers, and later summarized in *Excel* spreadsheets. Thus, the step-by-step for the data collection was: access to SISCAN through the address www.siscan.saude.gov.br, selection of item "manage tests", then "test data" (field selected: cervix cytopathology), followed by the "status" selection (field selected: released), and, finally, select "requesting facility" and "period" (period from 01/01/2014 to 12/31/2014). The reports analyzed were only those already released to the users, with no risk of the access resulting in results change.

Thus, the study variables were those described in the system and that could influence the occurrence of cellular changes in the cervix: confirmed pregnancy, use of Intrauterine Device (IUD), use of contraceptive pill, bleeding after sexual intercourse, bleeding after menopause, use of hormone replacement therapy, signals suggestive of Sexually Transmitted Disease (STD), presence of microbiology, cellular changes and atypia. We should notice that the cytological findings were considered the reports results that showed: cytolysis, hypotrophy, dyskeratosis, macronucleosis, scute scales, macrocytosis, binucleation and perinuclear halos, because these were specific to the clinical pathology.

The theoretical referential that subsidized the interpretation and the discussion of the results was the National Policy of Female Healthcare (National Policy of Integral Care to Women's Health - PNAISM) in force in the

country in relation to reproductive health, in addition to the Primary Healthcare Booklet number 13, regarding the Cervix and Breast Cancer Control by the Health Ministry.^{8,14}

For the data analysis, we used the *Statistical Package for the Social Sciences* (SPSS) software, version 20.0. Initially, the descriptive statistics was used to calculate the frequencies, which made it possible to briefly describe the study phenomena. To study the association between the independent variables and the occurrence or not of the outcome, a bivariate analysis was performed at each determination level through the Pearson Chi-square tests, when the variables showed regular distribution, and the Fisher exact test for the non-parametric data.

The association intensity was assessed through *Odds Ratio* estimates. To control the effect of potentially confounding variables, we used the multivariate analysis (multiple logistic regression). For all inferential statistical tests, we used the pre-established significance level at $p < 0.05$. The adjustment quality was assessed through the *Hosmer-Lemeshow* test. The development of this research followed the ethical rules and directives provided in the National Health Council Resolution n° 466/12, exempting the use of the Informed Consent Form and approval in the Committee of Ethics and Research in humans of Federal University of Fronteira Sul (UFFS), under report n° 059401/2015 and CAAE n° 46421815.0.0000.5564.¹⁵

RESULTS AND DISCUSSION

1.157 cervical cytological test reports were reviewed. Of these, 70.1% (n = 810) were performed in women with ages ranging between 25 and 64 years, age group considered a target for the healthcare actions in the country. In addition, 22% (n = 254) of the tests were performed in women with ages ranging between 15 and 24 years and 8% over 65. There are several factors that directly or indirectly indicate that the screening of women younger than 25 has no impact on the reduction of occurrence of cervical cancer, once only 1,1% of the cases of invasive lesions occur in women until 24 years old.¹⁶ Similarly, there are less objective evidences on when women should stop collecting. There is a trend to increase the interval between collections in older women, as proposed in the World Health Organization (WHO) current recommendations. However, there are no objective data that screening is useful after the age of 65.¹⁷

The main characteristics of the women who were submitted to the cervical cytological test are shown in Table 1. It was possible to verify that 96.88% were performed for disease control and screening and 11.58% of the women had never been tested, with a statistical significance for the age group between 15 and 24 years.

Table 1 - Characteristics of women submitted to the collection of cyto-pathological material from the cervix, according to the age group. Chapecó/SC. 2015

Total	Age group (years)						Women's characteristics
	≥ 65	55 to 64	45 to 54	35 to 44	25 to 34	15 to 24	
							Test reason
1121	89	107	108	207	364	246	Screening
22	4	4	3	5	2	4	Follow-up
14	0	2	2	3	3	4	Repetition
134	10	5	8	4	19	88*	Never tested
12	0	0	0	5	6	1	IUD user
549	0	0	20	104	255	170	Pill user
11	0	0	0	1	2	8	Confirmed pregnancy
01	0	0	1	0	0	0	Radiotherapy treatment
22	4	8*	4	2	2	2	Hormone replacement therapy
35	0	4	3	7	14	7	Bleeding after sexual intercourse
08	2	5*	1	0	0	0	Bleeding after menopause
30	0	0	3	5	13*	9	Signals suggestive of STD

* Significant difference between the sample age group to $p < 0,05$ (Fisher's exact test with Yates correction).

In spite of the evident benefits in the screening test, it is believed that 40% of the Brazilian women were never tested due to factors associated to fear or distress, or because of the difficulty to access the service.¹⁸ We emphasize that the women's age group below 25 who were never tested in this study were not considered priority in the screening actions for cervical cancer control. However, some authors emphasize the recommendation to test all women at the start of sexual activity, with multiple partners, tobacco use and repetitive genital infections.^{3,19}

Women who reported bleeding after menopause and used hormone replacement therapy in this study comprised the age group between 55 and 64 years, with statistical significance for this group. A similar result was found in the study by Silva and collaborators (2015). The cervix is highly sensitive to estrogens, when compared to other areas of the reproductive system in this age group, inducing the propagation of the HPV virus.²⁰

About the test results characteristics, 99.01% of the sample selected were satisfactory, with statistical significance for unsatisfactory samples in women over 65. In 90.06% of the reports, the cervix visualized during the collection was normal and Transformation Zone (TZ) cells were present in 74.76% ($n = 865$) of the tests (Table 2).

Table 2 - Characteristics of the cyto-pathological test results for cervical cancer control. Chapecó/SC, 2015

Total	Age Group (years)						Variable
	≥ 65	55 to 64	45 to 54	35 to 44	25 to 34	15 to 24	
							Sample assessment
1146	90	112	111	213	367	253	Satisfactory
11	3*	1	2	2	2	1	Unsatisfactory
							Appearance of the visualized cervix
1042	75	99	105	194	336	233	Normal
80	5	3	3	15	33*	21	Changed
							Sample epithelium
279	59*	62*	36	34	49	39	Squamous
662	23	41	54	137	245	162	Glandular
203	8	8	21	42	73*	51	Metaplastic
							Representativeness ZT
865	31	50	74	178	318	214	Present
281	59*	62*	37	35	49	39	Absent

* Significant difference between the sample age group to $p < 0.05$ (Fisher's exact test with Yates correction).

A similar result was found in a study conducted in Maranhão, in which TZ was represented in 64,2% of the tests. However, some authors state that, to consider a collection of good quality and reliability, this zone should be represented in all tests, except for women submitted to hysterectomy.²¹⁻² It should be emphasized that the absence of glandular epithelium, as well as the presence of TZ, had statistical relation in women over 55, in light of the results found in a study conducted in São Paulo.²² These findings may be related to the difficulty in performing the collection in women in this age group, once, in this period, there is a shortage of estrogen, resulting in the reduction of the number of squamous and glandular cells available for sampling. Also, the retraction of the endocervical mucosa and the external orifice is stenotic, which makes it difficult to collect the material.²³

The sample was considered satisfactory if it had cells in sufficient amount, well distributed, stained and fixed, that allowed good visualization and completion of a diagnosis, thus not considering the epithelial representativeness collected.²¹ Thus, the presence of Metaplastic or endocervical cells that represent the TZ is considered an indication of the test quality, since most of the lesions starts in this location.^{18,21}

We emphasize that the modified cervix visualized during the collection, as well as the presence of Metaplastic epithelium, associated to the diagnosis of squamous metaplasia, was more prevalent in women between 25 and 34 years old, with statistical significance for this group. Similar data were found in a study conducted in Rio Grande do Norte, where 65% of the women with this diagnosis were aged between 20 and 39.²⁴ Squamous metaplasia is a transformation process of the squamous epithelium that occurs predominantly in younger women, making them more vulnerable to the development of cervical intraepithelial lesions and the risk of infection with Human Papillomavirus (HPV).²⁵⁻⁶

The resulting cellular changes in the cytopathological reports in the study sample are shown in Table 3. The benign changes were more frequent, with emphasis to inflammations (18.9%), followed by the main cytopathological findings (11.8%). The prevailing microbiological agent was *Lactobacillus sp* (60.3%), while the infectious agent was *Gardnerella vaginalis* (16.8%).

Table 3 - Cellular changes in the cytopathological test of the study population. Chapecó/SC, 2015

%	n	Variables
Microbiological agents		
60.3	698	<i>Lactobacillus sp</i>
0.2	02	Cocos
5.1	59	Bacilos
Infectious agents		
3.8	44	<i>Candida albicans</i>
0.1	01	<i>Chlamydia sp</i>
16.8	195	<i>Gardnerella vaginalis</i>

(To be continued)

(Continuation)

%	n	Variables
0.2	02	<i>Trichomonas vaginalis</i>
7.4	86	> 2 associated
Benign cellular changes		
18.9	219	Inflammation
8.1	94	Atrophy with inflammation
5.8	67	Immature squamous metaplasia
11.8	135	Cytological findings*
10.2	117	> 2 associated
Atypias in squamous cells		
1.0	12	Low degree intraepithelial lesion
0.3	04	High degree intraepithelial lesion
1.6	19	Atypias of undetermined significancy

* Cytolysis, hypotrophy, dyskeratosis, sceratose, macronucleosis, scute scales, macrocytosis, binucleation and perinuclear halos.

The results in this study were similar to other studies conducted in Campo Grande and Maranhão, where inflammations were more frequent, with 22.5% and 19.5% proportions, respectively.²⁷⁻⁸ Inflammations are considered a benign cellular change in the epithelial cells that can be caused by the action of physical agents, whether radioactive, mechanical or thermal, chemical agents, such as abrasive or chemotherapy drugs, or acidity of the vagina on the glandular epithelium and can, occasionally, be caused by the IUD use and pathogens not identified in the test.²³ Clinically, they increase the vaginal content, causing pruritus, hyperemia and, sometimes, unpleasant odor.²⁹ These signals and symptoms are the main reasons that lead the women to search for healthcare services for gynecological consultation.²⁹

The cytological findings in this study, such as cytolysis, dyskeratosis, macrocytosis, macronucleosis, binucleation, among others, are morphological cellular changes that facilitate the HPV virus infection.³⁰ The microbiological findings, such as *Lactobacillus sp*, were also the most frequent in other studies.²⁴ However, this finding is considered normal, since this microbium is part of the vaginal microbiota and does not characterize infections that need treatment.^{27,31} As regards infectious findings, *Gardnerella vaginalis* was also the most frequent, similarly to another study.²⁸ Its occurrence can be caused by the change in the normal vaginal flora increasing the pH and resulting in a grayish-colored, foul-smelling vaginal discharge, that needs to be treated.³²

The association between the studied variables and the cellular alterations found in the epithelium of the sample is shown in Table 4. Age between 25 and 64, use of contraceptive pill, previous use of Hormone Replacement Therapy (HRT), presence of transformation zone, Metaplastic epithelium and cervix appearance are associated to the risk of cellular changes (Table 4).

Table 4 - Bivariate analysis of the association between the study variables from cytopathological tests for cervix cancer control and the cellular changes found in the sample epithelium. Chapecó/SC, 2015

p-Value	Epithelial Cellular Change				Study variables
	No (n = 479)		Yes (n = 667)		
	n	%	n	%	
0.0005*	74.3	356	67.0	447	Yes
	25.7	123	33.0	220	No
0.550	0.8	4	1.2	8	Yes
	99.2	475	98.8	659	No
0.000*	54.5	261	42.9	286	Yes
	45.5	218	57.1	381	No
0.108	90.2	432	87.1	581	Yes
	9.8	47	12.9	86	No
0.418	0.2	1	0.0	0	Yes
	99.8	478	100	667	No
0.597	1.0	5	0.7	5	Yes
	99.0	474	99.3	662	No
0.257	2.3	11	3.4	23	Yes
	97.7	468	96.6	644	No
0.476	0.4	2	0.7	5	Yes
	99.6	477	99.3	662	No
0.005*	2.5	12	1.2	8	Yes
	97.5	467	98.8	659	No
0.005*	75.6	362	75.4	503	Present
	24.4	117	24.6	164	Absent
0.009*	94.4	439	91.8	595	Normal
	5.6	26	8.2	53	Modified
0.000*	2.9	14	28.4	189	Yes
	97.1	465	71.6	476	No
0.0886	1.7	8	3.3	22	Yes
	98.3	471	96.7	645	No

* Significant difference between the sample age group to $p < 0.05$ (Fisher's exact test with Yates correction).

Finally, Table 5 shows the results of the multiple logistic regression analysis to control the effects of potentially confounding variables. The variables that appear to be statistically associated with the epithelial cellular changes in this final model were: age between 25 and 64, contraceptive use, HRT and presence of Metaplastic epithelium.

Table 5 - Logistic regression of factors associated to epithelial cellular changes of women submitted to cytopathological test. Chapecó/SC, 2015

p-value	95% IC	Adjusted OR	Variable
0.0019	(0.91 - 1.93)	1.4	Age 25 - 64
0.0000	(1.47 - 2.48)	1.9	Contraceptive use
0.0270	(1.15 - 10.2)	3.4	Hormone replacement therapy
0.0000	(0.38 - 2.76)	1.3	Metaplastic epithelium

In this study, women aged 25-64 had 1.4 times more chances to develop a cellular change in relation to the other women's groups. As previously shown, the incidence of serious cellular changes, such as cervical cancer, is low in the population of women under 25, and there are no signs that show that screening is useful after the age of 65.⁸

As regards the use of contraceptive pill, it was observed that its use resulted in almost twice the chances of having epithelial cellular changes, similar to the one found in another study, in which the risk of lesions was 2.42 times in the women that used it for more than 10 years.³³ However, other researches did not show a significant association between the oral contraceptive use and the presence of cellular changes.³⁴

The oral contraceptives alone have no effect on the progression or development of cervical lesions, but they can act in synergy, increasing the susceptibility to develop high-degree lesions in women infected with HPV.³⁵ Also, they can

result in higher frequency of unprotected sexual intercourse, putting the women at risk of acquiring other STDs.³⁶

As regards the epithelium represented in the sample, it was possible to observe that women that had metaplastic epithelium had 1.3 times more chances to develop cellular changes in the cervix. This finding can be associated with the greater infection propensity of this epithelium due to the cell susceptibility, especially to the oncogenic HPV infection that needs replication and differentiation of the metaplasia for its own multiplication and survival.²⁶ HRT was also a relevant factor for this study, showing that women submitted to this therapy had a 3.4 higher risk of cellular changes. This therapy is the administration of isolated estrogen and, until now, the scientific evidence identified in relation to its use in the literature was the association with the risk of breast cancer in women in menopause, and its association with cellular changes predictive of cervical cancer was not possible.³⁷

CONCLUSION

In this study, it was possible to identify a few factors that influenced the occurrence of cellular changes in the cervix through the analysis of the cytopathological tests. If, on one side, the age between 25 and 64, the use of oral contraceptive, use of HRT and the presence of metaplastic epithelium acted as risk factors for the development of these lesions, on the other side, the fragility in screening can evidence failures in the efficiency of actions and services in clinical practice in primary care. In addition, the presence of metaplastic epithelium in this study was associated with a higher frequency of visibly changed cervix.

Although cytology is a screening test for lesions predictive of cervical cancer, the analysis of the tests also made it possible to identify the presence of more frequent infectious agents, such as *Gardnerella vaginalis*, as well as to identify microorganisms in the vaginal flora and cytological findings that make the uterine epithelium more susceptible to the invasion by potentially oncogenic agents.

In this context, nursing has a central role in the insertion of new behaviors and routines in the provision of care in primary care when dealing directly with the demands from these women when building a unique therapeutic plan based on the health protection and promotion actions in force in the country.

The findings in this study reinforce the importance of the periodical performance of the cervical cytopathological test, because it acts as a safe and efficient tool to be used and disseminated to all women, especially those aged 25-64 and who started sexual activity. However, we should notice that the reports assessed were only those in the public healthcare system, which means a partial vision of reality, characterizing a study limitation. We suggest that future researches use other basic care indicators that can be influenced by this care model.

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