Interobserver Agreement in Cytological Diagnosis of Atypical Squamous Cell of Undetermined Significance-Cannot Exclude a High-Grade Lesion and High-Grade Squamous Intraepithelial Lesions in Cervical Lesions

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Concordância Interobservador no Diagnóstico Citológico de Atipia Escamosa de Significado Indeterminado Favorecendo Lesão de Alto Grau e de Lesão Intraepitelial Escamosa de Alto Grau nas Lesões do Colo Uterino

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ABSTRACT

Introduction: The Papanicolaou test is an important screening exam for cervical carcinoma. The cytological diagnosis of atypical squamous cell of undetermined significance cannot exclude high-grade lesion is the category with the least interobserver agreement. **Objective:** Evaluate the interobserver agreement for the ASC-H and high-grade squamous intraepithelial lesions (HSIL) categories at a teaching hospital and to estimate ASC-H's capacity to predict higher grade lesions. **Method:** Smears from patients admitted from 2007 to 2015 whose original diagnosis was made by one pathologist, in addition to colposcopy and biopsy, when indicated, made by one gynecologist were collected in the Pathologic Anatomy Service of the hospital. The cytology was reviewed by two other pathologists separately and blindly. Both reviewers had access to data about age at the moment of the diagnosis in order to reproduce the clinical diagnosis. **Results:** There were 65.1% smears considered as ASC-H and 34.9%, as HSIL. The reviews concurred simultaneously with the original diagnosis in 54.7% of the cases. The *kappa* indexes for both categories and only for ASC-H were, respectively, 0.46 and 0.49 (moderate agreement). 68.3% of the smears primarily described as ASC-H resulted in higher grade lesions in histology. **Conclusion:** The data showed a moderate agreement between the pathologists for the ASC-H's diagnosis. It is important to highlight that ASC-H matched with higher grade lesions at the histology, needing follow-up as HSIL.

Key words: uterine cervical neoplasms; observer variation; Papanicolaou test; squamous intraepithelial lesions.

RESUMO

Introdução: O exame de Papanicolau é uma importante ferramenta na triagem do carcinoma do colo uterino. O diagnóstico citológico de atipias celulares escamosas de significado indeterminado favorecendo lesão de alto grau (ASC-H) é a categoria de menor concordância interobservador. **Objetivo:** Avaliar o grau de concordância interobservador para os diagnósticos de ASC-H e de lesões intraepiteliais escamosas de alto grau (LIEAG) em um hospital terciário e avaliar a capacidade do diagnóstico de ASC-H para predizer lesões de maior grau. **Método:** Foram coletadas lâminas de pacientes atendidas entre 2007 e 2015 no Serviço de Anatomia Patológica do hospital, com diagnósticos originais de ASC-H ou LIEAG realizados pelo mesmo patologista, colposcopia e biópsia, quando indicadas, pelo mesmo ginecologista. Essas citologias foram posteriormente revisadas por outros dois patologistas separadamente e às cegas. Ambos tiveram acesso a dados sobre idade no momento do diagnóstico para reproduzir o diagnóstico da prática clínica. **Resultados:** Houve 65,1% de lâminas listadas com ASC-H e 34,9% com LIEAG. As duas revisões concordaram concomitantemente com o diagnóstico original em 54,7%. Os índices *kappa* para os dois diagnósticos e somente para ASC-H foram, respectivamente, 0,46 e 0,49 (concordâncias moderadas). Das lâminas originalmente interpretadas como ASC-H, 68,3% resultaram em lesões de maior grau na histologia. **Conclusão:** Os dados mostraram uma concordância moderada entre os patologistas para o diagnóstico de ASC-H. É importante destacar que o diagnóstico de ASC-H correspondeu à lesão de maior grau de malignidade na histologia, demonstrando que essas lesões devem ser seguidas clinicamente como LIEAG.

Palavras-chave: neoplasias do colo do útero; variações dependentes do observador; teste de Papanicolau; lesões intraepiteliais escamosas.

RESUMEN

Introducción: La prueba de Papanicolaou es un importante examen de detección del carcinoma del cuello uterino. El diagnostico citológico de las células escamosas atípicas, no se descarta una lesión de grado alto (ASC-H) es la categoría de menor acuerdo interobservador. **Objetivo:** Los objetivos de este estudio fueron evaluar el grado de concordancia interobservador para los diagnósticos de atipias escamosas de significado indeterminado favoreciendo lesión de alto grado (ASC-H) y de lesiones intraepiteliales escamosas de alto grado (LIEAG) en un hospital terciario de Curitiba (PR) y evaluar la capacidad del diagnóstico de ASC-H de predecir las lesiones de mayor grado. **Método:** Se recogieron del Servicio de Anatomía Patológica del hospital las láminas de pacientes atendidas entre 2007 y 2015, con diagnósticos originales de ASC-H o LIEAG realizados por el mismo patólogo y colposcopia y biopsia, cuando indicadas, por el mismo ginecólogo. Esas citologías fueron revisadas después por otros dos patólogos separadamente y a ciegas. Ambos tuvieron acceso a datos sobre edad en el momento del diagnóstico para reproducir el diagnóstico de la práctica clínica. **Resultados:** Hubo el 65,1% de las láminas señaladas con ASC-H y el 34,9%, con LIEAG. Las revisiones concordaron concomitantemente con el diagnóstico original en el 54,7%. Los índices *kappa* para los dos diagnósticos y solamente para ASC-H fueron, respectivamente, 0,46 y 0,49 (concordancias moderadas). De las láminas originalmente interpretadas como ASC-H, 68,3% resultaron en lesiones de mayor grado en la histología. **Conclusión:** Hubo una concordancia moderada entre los patólogos para la categoría ASC-H. Se destaca también la correspondencia de ASC-H con lesiones de mayor grado en la histología, lo que dirige su seguimiento clínico como LIEAG.

Palabras clave: neoplasias del cuello uterino; variaciones dependientes del observador; prueba de Papanicolaou; lesiones intraepiteliales escamosas.

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INTRODUCTION

Cervical carcinoma is caused by the persistent infection of some oncogenic groups of the human papilloma virus (HPV) and is one of the most frequent tumors in the female population and one of the leading causes of death by cancer in Brazilian women[1]. HPV infection is the most common sexually transmitted disease (STD) worldwide and great part of sexually active individuals will have contact with the virus in some moment of the life[2]. The National Cancer Institute José Alencar Gomes da Silva (INCA) estimated for each year of the triennium 2020-2022 16,710 cases in Brazil[1]. Thus, instrumental tools to screen precursor lesions are important to allow early interventions in the tumor evolution.

The cervical cytologic exam (Papanicolaou test) is a screening tool for women exposed to the risk of developing cervical carcinoma. In Brazil, the Ministry of Health recommends screening at 25 years or three years after the first sexual activity, repeating the test once a year in the first two years and triennially thereafter. After 65 years, had the two initial tests been normal, screening can stop[3].

Pap smear has some particularities impeding the actual detection of this carcinoma, possibly leading to undertreatment of women with potentially aggressive lesions and overtreatment of borderline or low-grade malignancy eventually causing psychological damages and increase of public expenses[4]. The example is the low diagnostic agreement of pathologists about the cytologic category of atypical squamous cells of undetermined significance-cannot excluded high-grade lesion (ASC-H).

Studies indicate that the grade of diagnostic agreement for ASC-H is the lowest of all diagnostic categories of cytologic tests[5-7]. In 2001, The Bethesda Interobserver Reproducibility Study (BIRST)[6] identified that ASC-H had the worst reproducibility (22.4%) of the Bethesda System categories. In 2014, the same methodology was utilized to carry out the BIRST-2[7], when the interobserver diagnostic agreement more than doubled for ASC-H (60%). It is clear that cytopathologists should increase the utilization of the Bethesda System to reach improved consensus on reading cervical cytology.

Thus, the objective of the present retrospective and observational study was to assess the degree of interobserver agreement of ASC-H diagnosis and high-grade squamous intraepithelial lesion (HSIL) (in this case, when borderline outcome was detected in follow-up) among pathologists of the "*Complexo do Hospital de Clínicas da Universidade Federal do Paraná* (CHC-UFPR)". Additionally, the ability of the ASC-H diagnosis to predict lesions of higher malignancy grade in the histopathological test.

METHOD

The Institutional Review Board of CHC-UFPR approved the study, number CAAE: 96028318.1.0000.0096. The Informed Consent Form was waived because the data were obtained from the Pathological Anatomy Service (SAP) of CHC-UFPR. Analytical, observational, cross-sectional and retrospective study.

The files of the cervical preventive tests of patients diagnosed with ASC-H or HSIL consulted at the ambulatory of tocogynecology of the hospital were obtained from CHC-UFPR's SAP between January 2007 and December 2015. The HSIL-diagnosed smears included are of patients diagnosed as ASC-H at some moment during follow-up. In these cases, the first colposcopy after the diagnosis of ASC-H did not show abnormal findings and the squamocolumnar junction (SCJ) was not visible or partially visible being necessary to investigate the endocervical canal. Since the result of this test was negative, new cytology and colposcopy were indicated in six months, when the diagnosis of HSIL was completed. Both the smears of ASC-H and HSIL were originally evaluated by the same physician pathologist of the service and classified as "original analysis".

Slides from patients whose clinical data were not identified in the database of the ambulatory of tocogynecology or from CHC-UFPR's SAP were excluded and those whose analysis was not possible due to deterioration or discoloring.

Two skilled cytopathologists of the Medical Pathology of CHC-UFPR reviewed the slides. The first reviewer is member of the International Academy of Cytology (IAC) (IAC) and the diagnoses are mentioned in the text as "first review". The second reviewer is affiliated to IAC and its diagnoses are quoted as "second review".

Two blinded cytopathologists reviewed the cases independently, the "original analysis" or the histology from cold-knife conization was unknown to the reviewers. Both had access to clinical information about the age at the diagnosis and menopause status when available in order to reproduce the routine of the clinical practice. The review of these cases followed the terminology recommended by the Bethesda System[6] and the Brazilian Nomenclature for Cytology Reports in use by the hospital's SAP where NIC I (grade I intraepithelial cervical neoplasm) was referenced as low-grade squamous intraepithelial lesion (LSIL) and the terminologies NIC II and NIC III (grade II and III intraepithelial cervical neoplasms) as HSIL.

Resident-physicians of gynecology and cervical pathology supervised by one skilled lead-colposcopist performed the colposcopy of the patients diagnosed with ASC-H and HSIL enrolled in this study. Samples

whose colposcopy results were not supervised by the lead-colposcopist were discarded because this outcome could lead to a wrong diagnosis.

For negative colposcopy where the area modified to be biopsied was unidentified, the patient was submitted to oncotic cytology follow-up for six months and the result was considered as "Outcome". The biopsied patients with negative colposcopy or LSIL were discharged and referred to BHU (Basic Health Unit) and the result of the colposcopy-directed biopsy was concluded as "Outcome". The HSIL patients after the biopsy were submitted to cold-knife conization. The histological diagnoses of the biopsies and cold-knife conization as "Outcome" were obtained from databases of CHC-UFPR's SAP.

The epidemiologic analysis of age at the diagnosis utilized the information of the database of CHC-UFPR's SAP.

Mean, minimum and maximum values and standard-deviation (SD) were adopted to describe the quantitative variable and for the categorical variables ("cytologic diagnoses of the first analysis", "cytologic diagnoses of the second analysis", "cytologic diagnoses of the original analysis" and "cytologic diagnoses of the Outcome"), frequencies and percentage were calculated. The binomial test was adopted to compare the reviews for agreement with the original analysis. The statistic kappa (κ) was calculated to evaluate the reliability of the cytologic diagnoses of the two analyzes according to the criteria: non-significant for values lower than 0; weak between 0 and 0.2; fair between 0.21 and 0.4; moderate between 0.41 and 0.6; strong between 0.61 and 0.8 and almost perfect between 0.81 and 1. Confidence intervals of 95% were utilized and values of $p<0.05$ were considered statistically significant. The data were analyzed with software Stata/SE v.14.1. StataCorpLP, USA.

RESULTS

From January 2007 to December 2015, 21,041 slides of uterine cervical cytology were analyzed at CHC-UFPR's SAP, of which 0.86% (181) were classified as ASC-H and 1.39% (293) as HSIL.

The same pathologist diagnosed the 181 ASC-H and 293 HSIL slides in SAP database – this was relevant for the analysis of only one expert to be retested in this study. Of these 474 samples, 107 did not have colposcopy register at the database and were excluded from the process at once. For the samples to be revaluated, it was necessary to identify the result of the colposcopy during the patients' follow-up, being this the diagnostic outcome. Of the remaining 367,175 had colposcopy evaluation unsupervised by the lead-colposcopist. Only 172 of the remaining 192 smears were reviewed as 20 slides were not found with the same number of the database of the cervical pathology or were unfit for evaluation (Figure 1).

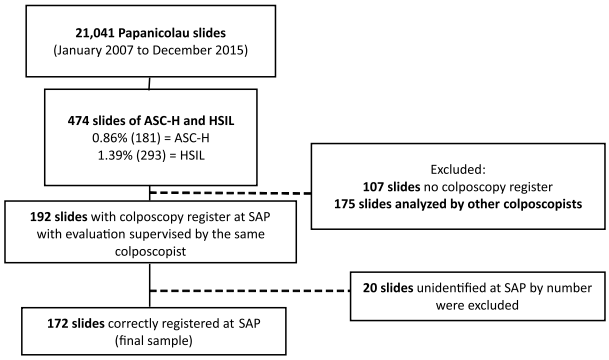

Figure 1. Flowchart of the study sampled

Captions: ASC-H = atypical squamous cells of undetermined significance-cannot exclude high-degree lesion; HSIL = high-grade squamous intraepithelial lesion; SAP = Pathology Anatomy Service.

The 172 slides selected are from 163 patients since nine slides are repeated cytologic exams followed up according to the recommendation of the Ministry of Health and adopted by the hospital.

Of the 172 smears analyzed, the prevalence of ASC-H in the original analysis is 65.1% (112 smears) and 39.4% (60 smears) HSIL.

The analysis of the agreement between the results of the original and the first review (Table 1) concluded that 61.6% were concordant (CI 95%; [54.4% - 68.9%]).

The agreement of the first review concluded that 72.32% is ASC-H and 41.67% HSIL. For the diagnostics of ASC-H

Table 1. Agreement between the reviews and original analysis

Agreement	First review		Second review	
	Absolute quantity	Relative quantity	Absolute quantity	Relative quantity
No	66	38.4%	51	29.7%
Yes	106	61.6%	121	70.3%
Total	172	100%	712	100%

of the original analysis, the first reviewer concluded that 22.32% of the cases were low-grade malignant lesions (negative = 4.46%; ASC-US = 16.07%; and LSIL = 1.79%) and 3.57% as high-grade lesions. 1.79% of the ASC-H diagnoses were interpreted as AG-US and 1.67% of the originally reviewed as HSIL (Table 2).

The diagnostic agreement was 70.3% (CI 95%; [63.5% - 77.2%]) in the comparison between the results obtained in the original analysis and the second review (Table 4).

The agreement for ASC-H was 73.2% between the concordant diagnostics of the second review and the original analysis while for HSIL, 65%. Only 10.8% of the ASC-H slides of the original analysis were interpreted as low-grade lesions (negative = 4.5%; ASC-US = 6.3%) and 16.1% of these samples were concluded as high-grade lesions. The original diagnoses of HSIL could predict lesions of higher grade in 20% of the occasions, while 15% would actually be lower-grade lesions (negative = 5%; ASC-US = 5%; LSIL = 5%). No sample was classified as AG-US after this revaluation (Table 2).

The two reviews agree with the original in 54.6% of the cases and non-concordant in 22.7%. In addition, only the first review agreed with the original diagnosis in 7% while in 15.7%, only the second review was concordant (p=0.024).

The reviewer's agreement is moderate with value of κ equal to 0.46 (CI 95%; [0.36 – 0.56]). The diagnoses with the best agreement within 68.6% of the concordant diagnoses were ASC-H and HSIL (81 and 27 slides, respectively). On the other hand, the second reviewer interpreted 25 of the 111 slides as high-grade lesions classified as ASC-H by the second reviewer. Only five of the 140 slides with diagnosis of higher-grade (ASC-H and HSIL) by the first reviewer were classified as low-grade by the second (negative = 2; ASC-US = 2; and HSIL = 1) (Table 3). The specific κ for ASC-H and HSIL were, respectively, 0.49 and 0.52 – moderate agreement.

Of the 151 slides with high-grade lesions (ASC-H and HSIL) according to the second review, only 13 were interpreted as low-grade (negative = 1; ASC-US = 10; and HSIL = 2) by the first. And of the 94 samples with ASC-H according to the second review, only two were concluded as HSIL by the first (Table 3).

142 slides of the 172 of this study were interpreted as ASC-H in any of the three reviews. The analysis of the outcome of these samples confirmed by histopathological exam showed that 68.3% (97/142) of the cases of ASC-H corresponded to high-grade lesions of malignity (HSIL = 61.3%; Microinvasive SCC = 1.4% and invasive squamous cell carcinoma = 5.6%). In counterpart, 23.2% of the patients had negative results based in the golden standard exam (Table 4).

In the same context, 6.3% of the patients did not submit to the golden-standard exam – 2.8% because they missed the follow-up prescribed by the physician

Table 2. Comparison between the results of the reviews and original assessment

Distribution of the results of the review		Distribution of the results of the original analysis			
		ASC-H		HSIL	
		Absolute quantity	Relative quantity	Absolute quantity	Relative quantity
First Review	(-)	5	4.46%	0	0.00%
	AG-US	2	1.79%	1	1.67%
	ASC-H	81	72.32%	30	50.00%
	ASC-US	18	16.07%	2	3.33%
	HSIL	4	3.57%	25	41.67%
	LSIL	2	1.79%	2	3.33%
	Total	112	100.00%	60	100.00%
Second Review	(-)	5	4.50%	3	5.00%
	ASC-H	82	73.20%	12	20.00%
	ASC-US	7	6.30%	3	5.00%
	HSIL	18	16.10%	39	65.00%
	LSIL	0	0.00%	3	5.00%
	Total	112	100.00%	60	100.00%

Captions: (-) = negative; AG-US = atypical glandular cells of undetermined significance; ASC-US = atypical squamous cells of undetermined significance; ASC-H = atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; HSIL – high-grade squamous intraepithelial lesion.

Table 3. Distribution of the absolute agreement between the first and second review

Absolute distribution of the second review	Absolute distribution of first review						
	(-)	AG-US	ASC-US	ASC-H	LSIL	HSIL	Total
(-)	2	0	4	2	0	0	8
AG-US	0	0	0	0	0	0	0
ASC-US	2	0	6	2	0	0	10
ASC-H	0	2	9	81	0	2	94
LSIL	0	0	0	1	2	0	3
HSIL	1	1	1	25	2	27	57
Total	5	3	20	111	4	29	172

Captions: (-) = negative; AG-US = Atypical glandular cells of undetermined significance; ASC-US = Atypical squamous cells of undetermined significance; ASC-H = Atypical squamous cells of undetermined significance-cannot exclude a high grade lesion; LSIL = Low-grade squamous intraepithelial lesion; HSIL – High-grade squamous intraepithelial lesion.

Note: The absolute quantities of smears with diagnostic agreement after review of two observers are in gray.

Table 4. Distribution of the results per outcome

Outcome	Absolute quantity	Relative quantity
Loss of follow-up	4	2.8%
(-)	33	23.2%
ASC-US	5	3.5%
LSIL	3	2.1%
HSIL	87	61.3%
Microinvasive SCC	2	1.4%
Invasive SCC	8	5.6%
Total	142	100.0%

Captions: (-) = negative; ASC-US = atypical squamous cells of undetermined significance; LSIL = low grade squamous intraepithelial lesion; HSIL = high grade squamous intraepithelial lesion; Microinvasive squamous cell carcinoma (SCC); Invasive squamous cell carcinoma (SCC).

and 3.5% because of the repetition of other cytologic exam revealing low-grade malignancy lesion (ASC-US) (Table 4).

At last, the mean age of the patients diagnosed with ASC-H in this study was 40.7 years (± 13.5) ranging from 19 to 84 years.

DISCUSSION

The new Bethesda System of 2014 defined three main principles according to which, the terminology should express clinically important laboratory information reported to the physician in charge of the patients; standardized and reasonably reproducible among different pathologists and laboratories, flexibility to match to different laboratories and locations and reflecting the current knowledge of cervical neoplasm[8].

The prevalence of ASC-H and HSIL in Brazil is respectively 0.2% and 0.26% among all tests and 8.8% and 9.1% for tests with alterations[3]. Higher prevalence of borderline diagnosis (0.86%) and HSIL (1.39%) among all tests can be explained by the fact that the Ambulatory of Tocogynecology of CHC-UFPR is reference for lower genital tract and patients referred by the BHU with previous exams with alterations.

With predominance of borderline smears (65.1% of ASC-H *versus* 34.9% of HSIL), it was attempted to evaluate the level of diagnostic agreement among pathologists-physicians at CHC-UFPR to investigate the technical reproducibility. The agreement between the original and first review was 61.16%, slightly lower than the unanimity of the second review (70.3%) and the diagnostic agreement among reviews (68.6%).

In addition, the first review was more consistent with the original diagnoses of ASC-H than with HSIL (72.32% *versus* 41.67%, respectively) but also brought a high rate of suspected malignancy for these last results, classifying 50% of them as ASC-H, revealing the pathologist's more conservative approach. The second review showed diagnostic agreement with the original readings of ASC-H nearly similar to the first (73.2%). However, it showed more agreement with the smears originally analyzed as HSIL (65%), if compared with the first and identified 20% of these as ASC-H, concluding that this pathologist decided for a more innovative approach in the cytologic diagnostic. Comparing the results of the three reviewers, it was found evidence that the two reviews differ in relation to the likelihood of consistency with the original analysis (p=0.024), both agreeing only in nearly half of the cases (54.6%).

These data indicate that even with actual expected non-agreement, the results of the reviews tend to classify most of the slides as high-grade squamous intraepithelial lesions (ASC-H and HSIL). It may portray what was recently addressed by Scheck et al.[9], when non-agreement

between cytology and histology exists, at least one result of high-grade malignancy calls for more investigation or even, revaluation. The 5-year follow-up of patients with cytologic diagnosis of ASC-H and HSIL showed 30% to 50% odds of evolution to malignant lesions.

The reviewers agreement for ASC-H and the original cytology of the patients were greater than the study BIRST-2 (60%)[7] has concluded. This finding corroborates the tendency found by the authors in relation to BIRST[6] that the diagnostic interobserver agreement of borderline diagnostic has increased. Some authors believe[5] that the experience of the observer is relevant for correct cytologic diagnostic. Others[10] point out possible determinants for the variability of the results: work overload and inherent diagnostic difficulty of the category of atypical undetermined, which emphasizes the necessity of good relation between the gynecologist and cytopathologist while pursuing quality exams.

Evidence exists[8] that morphologic characteristics of smears are more determinant than the academic or professional level of the observers (nucleolus prominence surrounded by neutrophils and nuclei augmented with mild presentations of chromatins – findings representative of tissue repair listed as aspects of malignancy lesions). Other authors[11] point out that continued sessions involving the discussion of discordant cases, review of smears and standardization of cytopathological criteria hold strong influence on the interobserver level of disagreement.

Similar to the findings of this study, other authors with analogous results attribute to the Bethesda system the good rates of diagnostic reproducibility[12], affirming that the criteria of this system can be assimilated and routinely applied. This concurs with the principle of flexibility of the terminology that should match several technical and regional contexts.

The diagnostic agreement between the two reviewers in this study was deemed moderate ($\kappa = 0.46$), showing good reproducibility. Moderate agreement between the reviewers was also reached in other studies [7,12] but present the category ASC-H as worst reproducibility too in the respective studies (specific κ between 0.19 and 0.38 – low to fair agreement)[5]. These data suggest that the terminology ASC-H still has low reproducibility among other diagnostic categories of this system.

In the current study, specific κ for ASC-H and HSIL were not that different and were considered of moderate agreement (0.49 and 0.52, respectively). The explanation for the augment of reproducibility of ASC-H and low reproducibility for HSIL is due to selection bias of the cases. Only smears originally diagnosed as ASC-H or HSIL (with borderline cytologic diagnosis during follow-up of these last cases) were considered, which may not represent a reliable sample of the reality. Similarly, measurement bias occurred in the review of the pathologists as they knew what the objective of the study was and possibly which slides they would analyze.

The frequency of HSIL was 6.31% and carcinoma, 7% for women with cytology of ASC-H. This prevalence is within the ranges from 12.2% to 68% (for HSIL) and 1.3% to 39% (for cervical carcinoma) as anticipated in the literature[3]. A core point of the study is that the rate of women who failed to follow the protocol recommended by the Ministry of Health was low (2.8%) compared to the current data. Pursuant to the most updated national literature[13], after the diagnosis of ASC-H, no conduct was adopted for 40.5% of women consulted in the State of Ceará. CHC-UFPR is a teaching hospital whose mission is to ensure a friendly environment for teaching, research and graduation and this can be seen as a potential determinant for proper adherence to follow-up the patients diagnosed with ASC-H in this study.

In concurrence with the World Health Organization recommendations, the predominant screening pattern in Brazil is opportunistic, the patients submit to cytopathologic exam when they seek for health services for other reasons. Consequently, almost 21% of the exams are off the recommended age-range[14]. With this, there is a group of women screened beyond the recommended and another group without any screening test, compromising the access of those who actually need to be screened and referred for diagnostic and precursor lesions. In the current analysis, 0.8% of the patients had less than 25 years but this can be underestimated as only slides with two categories were reviewed.

The mean age of the patients diagnosed with ASC-H was 40.7 years (± 13.5), ranging from 19 and 84 years. There were patients screened before 25 years (lower threshold screening for cervical carcinoma). Despite the evidence[15,16] of high odds of regression of pre-invasive lesions until 24 years of age, these patients were consulted according to the guidelines of the Ministry of Health[3].

The reviewers were aware that the objective was to review the interobserver agreement level for the diagnostic category ASC-H of the Bethesda System, which is an important limitation of the study. It may have induced the pathologists to interpret the findings as lesions of high malignancy and possibly contributing for low agreement of HSIL in comparison with the scientific community. An additional limitation was the exclusion of samples based in the selected criteria. The absence of these smears may have influenced the epidemiology, but it is important to strengthen that there were physical and diagnostic obstacles for this.

Despite the limitations, the study contributed to raise the awareness for continuous education in cervical cytology for the pathologists of CHC-UFPR. Emphasis should be given to the approach to lesions of undetermined significance, the category with higher disagreement among the reviewers (Table 3): nine diagnostics of ASC-US in the first review changed to ASC-H in the second. This disagreement leads to dissimilar clinical conducts and should be addressed exhaustively during education similarly to high-grade intraepithelial lesions for standardization of the reviewers' morphologic criteria.

CONCLUSION

There was moderate interobserver agreement of the diagnoses of ASC-H and HSIL. The specific agreement for ASC-H was moderate as well. The diagnosis of ASC-H corresponded to high-grade malignancy lesion in histology, indicating these lesions should be followed up as HSIL.

Continuous education in cervical cytology of the pathologists of CHC-UFPR is required to standardize the diagnoses of ASC-H and HSIL according to the Bethesda System.

CONTRIBUTIONS

All the authors contributed substantially for the study conception/design, collection, analysis and/or interpretation of the data, wording and critical review and approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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None.

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