

Atypical Squamous Cells—Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H): A Result Not to Be Ignored

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Abstract

Objective: The objective of this study was to determine the risk of a clinically significant lesion associated with the diagnosis of atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion (ASC-H) on cervical cytology (Pap smear).

Methods: This was a retrospective, observational, descriptive study. A computerized database containing cytologic and histologic information for the health region was used to identify women with a diagnosis of ASC-H on a Pap smear performed between January 1 and December 31, 2002. All pertinent pathology data (cytopathology, histopathology, and surgical specimens) were examined. Patients were excluded if they had a diagnosis of cervical cancer, adenocarcinoma in situ (AIS), or high-grade squamous intraepithelial lesion (HSIL) prior to the index Pap smear.

Results: During the study period, 727 of 241 841 Pap smears (0.3%) were reported as ASC-H in 655 patients. Ninety-one patients had a previous diagnosis of cervical cancer, AIS, or HSIL and were excluded from analysis, and 12 patients on review did not have ASC-H. There were no follow-up data for 35 of the remaining 552 patients, leaving 517 patients in the study group. In this group, the rates of histologically proven cervical lesions were 2.9% (15/517) for cervical cancer, 1.7% (9/517) for AIS, and 65.6% (339/517) for HSIL. Women undergoing a procedure that included histological examination were more likely to have a significant lesion discovered.

Conclusion: The diagnosis of ASC-H on Pap smear is associated with an appreciable risk of clinically significant disease. Patients with an ASC-H Pap smear result should undergo timely colposcopic and histologic assessment to rule out HSIL, AIS, and cervical cancer.

Résumé

Objectif : Cette étude avait pour objectif de déterminer le risque de voir apparaître une lésion significative sur le plan clinique associé au diagnostic de « cellules malpighiennes atypiques, ne peut

exclure les lésions intraépithéliales de haut grade histologique » (ASC-H) obtenu par cytologie cervicale (frottis de Pap).

Méthodes : Il s'agissait d'une étude descriptive, observationnelle et rétrospective. Une base de données informatisée, contenant des renseignements cytologiques et histologiques pour la région sanitaire à l'étude, a été utilisée afin d'identifier les femmes qui avaient obtenu un diagnostic d'ASC-H à la suite d'un frottis de Pap effectué entre le 1^{er} janvier et le 31 décembre 2002. Toutes les données pathologiques pertinentes (cytopathologie, histopathologie et prélèvements chirurgicaux) ont été examinées. Nous avons exclu les patientes qui avaient obtenu un diagnostic de cancer du col utérin, d'adénocarcinome *in situ* (AIS) ou de lésion intraépithéliale de haut grade histologique (LIHG) avant l'exécution du frottis de Pap index.

Résultats : Au cours de la période d'étude, 727 des 241 841 frottis de Pap (0,3 %) ont été signalés comme présentant des ASC-H chez 655 patientes au total. Quarante-vingt-onze patientes avaient déjà obtenu un diagnostic de cancer du col utérin, d'AIS ou de LIHG et ont été exclues de l'analyse; de plus, il s'est avéré, dans le cadre d'un réexamen, que 12 patientes ne présentaient pas d'ASC-H. Aucune donnée de suivi n'était disponible pour 35 des 552 patientes restantes, ce qui a fait en sorte que le groupe d'étude n'a compté que 517 patientes. Au sein de ce groupe, les taux de lésions cervicales prouvées par examen histologique ont été de 2,9 % (15/517) pour le cancer du col utérin, de 1,7 % (9/517) pour l'AIS et de 65,6 % (339/517) pour la LIHG. Les femmes se soumettant à une intervention qui comprenait un examen histologique étaient plus susceptibles de voir leur médecin découvrir une lésion significative.

Conclusion : Le diagnostic d'ASC-H obtenu par frottis de Pap est associé à un risque appréciable de maladie significative sur le plan clinique. Les patientes qui obtiennent un résultat d'ASC-H à la suite d'un frottis de Pap devraient se soumettre, en temps opportun, à une évaluation colposcopique et histologique afin d'écartier la possibilité d'une LIHG, d'un AIS et d'un cancer du col utérin.

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INTRODUCTION

Screening for and detection of pre-invasive disease have made cervical cancer a potentially preventable gynaecologic malignancy. Classifications of cervical cytology have assisted clinicians in selecting patients at risk for

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high-grade dysplasia and referring them for colposcopy. Particular attention has focused on the appropriate diagnosis and triage of results suggesting atypical squamous cells of undetermined significance (ASCUS). The 2001 Bethesda System for reporting results of cervical cytology modified the category of atypical squamous cells (ASC) into two qualifiers: "undetermined significance" (ASC-US) and "cannot exclude high-grade squamous intraepithelial lesion" (ASC-H).¹ The latter of these two categories indicates that atypical Pap smears are associated with either a true high-grade squamous intraepithelial lesion (HSIL) or its undetermined imitators.² Essentially, the new classification reflects an improved understanding of the association between equivocal findings, human papilloma virus (HPV) infection, and the likelihood of diagnosing HSIL on histopathology specimens. Indeed, high-risk HPV DNA has been shown to be present in 71% of ASC-H smears.³ In conjunction with the modified cytology classification, it has been suggested that colposcopic examination be performed in patients with an ASC-H cytologic diagnosis.^{4,5} Investigators initially described the probability of diagnosing histologic HSIL in women with an ASC-H smear as approximately 20% to 25%. Subsequent studies have reported that the risk of having HSIL histology with ASC-H cytology may be as high as 80% in a young population.^{6,7}

The purpose of this study was to determine the probability of finding a clinically significant lesion in women with a cytologic diagnosis of ASC-H, using a regional, population-based perspective.

METHODS

This study was a retrospective review. A computerized database containing cytologic and histologic information for the region was used to identify all Pap smears reported as ASC-H over a 12-month period (from January 1 to December 31, 2002). Relevant pathology data (cytology, histopathology) before and after the index ASC-H smear were extracted. For the purpose of this study, a clinically significant lesion was defined as an HSIL, cervical adenocarcinoma in situ (AIS), or invasive cervical carcinoma. Patients were excluded from analysis if they had a history of these clinically significant diagnoses prior to the ASC-H Pap smear. Patients were also excluded if no follow-up cytology or histology assessment was recorded in the laboratory database.

Ethics approval was obtained from the University of Alberta/Capital Health Research Ethics Board. Statistical analysis was performed using SAS version 8.2 (SAS Institute, Cary, NC). Significant associations between categorical variables were performed using a chi-squared

Table 1. Histology/cytology immediately following index ASC-H cytology

Initial Management	n (%)
Colposcopy and histology	423 (82)
LEEP	20 (3.9)
Cone biopsy	6 (1.1)
Cytology alone	63 (12)
Hysterectomy	5 (1.0)
Total	517(100)

ASC-H: Atypical squamous cells-cannot exclude high-grade lesion;
LEEP: loop electrosurgical excision procedure.

Table 2. Diagnosis on investigation following an ASC-H Pap smear (n = 517)

Diagnosis	Histology n (%)	Cytology Alone n (%)
Cervical cancer	15 (3.3)	0
Adenocarcinoma in situ	9 (2)	0
High-grade squamous intraepithelial lesion	339 (74.7)	11 (17.5)
Low-grade squamous intraepithelial lesion	33 (7.3)	4 (6.3)
Glandular dysplasia	2 (0.4)	0
Negative for dysplasia	56 (12.3)	48 (76.2)
Total	454(100)	63 (100)

ASC-H: Atypical squamous cells-cannot exclude high-grade lesion.

test. $P < 0.05$ was determined to be significant. Descriptive statistics were used to summarize demographic variables.

RESULTS

A total of 241 841 Pap smears were analyzed and reported in the region during the 2002 study period. Six hundred fifty-five patients (727 smears, or 0.3% of the total) had a cervical cytologic diagnosis of ASC-H. Ninety-one patients had a previous diagnosis of cervical cancer, adenocarcinoma in situ, or high-grade squamous dysplasia. Twelve patients did not have a definitive ASC-H diagnosis on further review, and for 35 patients, no follow-up information was available, leaving 517 patients available for analysis of relevant cytopathologic data. Each cytologic diagnosis of ASC-H was accompanied by a recommendation for follow-up. The recommendation in 93% of reports was for the patient to undergo colposcopic evaluation.

The median time from the initial ASC-H cytology diagnosis to first colposcopic/histologic examination was 59 days

Table 3. Diagnostic outcome in patients with ASC-H cytology

Any time post-ASC-H	≥ HSIL	< HSIL	Total (%)
Histology	363	91	454 (88)
No histology	11	52	63 (12)
Total	374	143	517 (100)

ASC-H: Atypical squamous cells—cannot exclude high-grade lesion; HSIL: high-grade squamous intraepithelial lesion

Table 4. Patient age and risk of a significant lesion

Age at index ASC-H Pap	≥ HSIL	< HSIL	Total
< 35 years	274	103	377
35–50 years	71	34	105
> 50 years	18	17	35
Total	363	154	517

ASC-H: Atypical squamous cells—cannot exclude high-grade lesion; HSIL: high-grade squamous intraepithelial lesion.

(range 21–70), and median patient age at time of the index ASC-H Pap smear was 29 years (range 15–82).

The type of cytologic or histologic follow-up that the study group of patients had as their next clinical investigation following an ASC-H Pap smear result is shown in Table 1. Of note, 82% of patients had an examination that included cervical histology as their next investigation. Interestingly, 12% of the study group had a Pap smear alone (that may have included colposcopy), and the remainder of patients (31) had a loop electrosurgical excision procedure (LEEP), cone biopsy, or hysterectomy as their initial management.

The follow-up diagnosis of the study group is outlined in Table 2. Of 517 patients, 374 (72%) had an initial follow-up diagnosis of HSIL, AIS of the cervix, or carcinoma of the cervix. Of these, 11 patients (3% of HSIL) had a diagnosis of HSIL made on cytology alone, and a “negative histology” diagnosis was made on cytology alone in 48/104 (46%) of patients.

As the Alberta cervical cancer screening program recommends a colposcopic examination for an ASC-H result,⁸ the number of patients undergoing colposcopy and histology during the study period was analyzed with respect to histologic outcome (Table 3). During the follow-up period, 88% (454/517) of patients had a colposcopic examination and histological assessment following an ASC-H Pap smear. Chi-squared analysis demonstrated a significant difference between those who underwent histologic sampling and

those who did not, and the rate of detection of HSIL or greater lesions ($P < 0.001$).

Patient age was examined as a risk factor for a diagnosis of HSIL in the ASC-H Pap (Table 4). An age of under 35 years was significantly associated with having HSIL, AIS or cervical cancer ($P = 0.025$).

Of 517 patients, 464 (89.7%) had a Pap smear result on record prior to the index (study) ASC-H Pap smear. When analyzed for outcome, having an abnormal Pap smear (i.e., AGC, ASC, or LSIL) was not associated ($P = 0.22$) with having HSIL, AIS or cancer.

DISCUSSION

The significance and optimal management of women with a cervical cytology report of “atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion” (ASC-H) has generated debate and stimulated clinical research.^{4,7,8} ASC-H was included as a new category of cytology nomenclature in the Bethesda 2001 terminology.^{1,3} Several studies have demonstrated a risk for high-grade dysplasia of 25% to 90% in patients with a Pap smear result of ASC-H.^{5–7} The change in nomenclature was a result of the realization by cytopathologists that slide interpretation of ASC (atypical squamous cells) was poorly reproducible and that a subset of ASC was associated with high-grade dysplasia on colposcopic histology.^{9–12} The present study confirms the significance of an ASC-H cytology result as 72% of patients had a subsequent histologic diagnosis of at

a least a high-grade lesion. It is also of clinical interest that in this group of patients with ASC-H, 15 had a histologic diagnosis of cervical cancer, and nine had AIS of the cervix. This emphasizes the potential significance of an ASC-H Pap smear result and further supports the recommendation for colposcopic examination and histologic sampling. It is of some concern that more than 12% of women in this study had only cytologic sampling as their initial management, despite colposcopy having been recommended for 93% of them by cytopathologists on the ASC-H cytology report. It could be argued that cytopathologists should recommend colposcopy for 100% of women who have ASC-H cytology. The failure to do so may reflect a lack of knowledge about appropriate follow-up of abnormal Pap smears; it is therefore a potential opportunity for further education of physicians and patients on the significance of an ASC-H Pap smear and for knowledge translation to change clinical care. However, it is possible that a portion of these 63 patients had a colposcopic examination that did not include histologic sampling. Potentially, experienced colposcopists may not always obtain a cervical biopsy if they are confident that their examination is negative.

The incidence of an ASC-H Pap smear during the one-year study period was 0.3% (727/241 841), a rate consistent with those in other studies.^{6,7} Almost 99% of the Pap smears performed in the region are processed and reported by a single laboratory (Dynacare Kasper Medical Laboratories), so this number may both reflect the proportion of the female population undergoing cervical cytologic screening and provide a reasonable estimate for the risk of ASC-H in a population setting. The median time from an ASC-H result to subsequent colposcopy was 59 days; this may be useful as a potential benchmark for the region and as a comparator for other jurisdictions. In the current health care environment where wait times for key procedures are under close scrutiny, the significance of an ASC-H result should be understood by health care administrators.

The findings in this study also demonstrated an increased rate of diagnosis of HSIL in patients who underwent colposcopy and histology compared with those who did not. The follow-up in the latter group of patients was with use of cytology alone and may also highlight the reality and challenges of Pap smear sensitivity. The present study, although having comprehensive cytologic and histologic

results, was limited by a lack of colposcopic examination records. In addition, if patients had subsequent follow-up outside the Capital Health region, this information was not available. Nevertheless, the information obtained in this study, providing an analysis of virtually all ASC-H results from a health region that captures 99% of the cytology, clearly demonstrates the risk for cervical disease associated with ASC-H. For women's health care providers, the message is unequivocal: an ASC-H cytology result requires referral to a practitioner skilled in colposcopic examination and the management of cervical disease.

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