

Low-Grade Pap Smears Containing Occasional High-Grade Cells as a Predictor of High-Grade Dysplasia

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Abstract

Objectives: This study compared clinical outcomes associated with Pap smear reports of atypical squamous cells cannot exclude HSIL (ASC-H) and those associated with "low-grade smears containing occasional cells suggestive of HSIL" (LSIL-H). In Alberta, women with ASC-H are referred for colposcopy, and women with LSIL are managed with follow-up Pap smears. LSIL-H is not included in the Bethesda classification and has not been characterized in terms of cytological features, reporting, management, and clinical course.

Methods: All ASC-H (n = 153) and LSIL-H (n = 189) Pap smears recorded in the regional laboratory information system between December 2000 and December 2001 were identified. All available histology for each associated patient over the subsequent two-year period was reviewed to determine if a high-grade histological lesion was ever confirmed in a biopsy, loop electrosurgical excision procedure (LEEP), or hysterectomy specimen.

Results: A high-grade squamous intraepithelial lesion was identified in 48% of the ASC-H group and 40% of the LSIL-H group ($P = 0.136$). Most of the HSIL histopathology was identified on the first colposcopic visit, suggesting that high-grade dysplasia may have been present at the time of the original Pap smear.

Conclusions: Pap smears reporting ASC-H and LSIL-H predict a high-grade squamous intraepithelial lesion with similar accuracy. Since approximately 40% of patients with an LSIL-H Pap smear have either concurrent or subsequent high-grade cervical pathology, we also recommend immediate referral for colposcopy in this group of patients.

Résumé

Objectifs : Cette étude a comparé les issues cliniques associées aux résultats de frottis de Pap « cellules malpighiennes atypiques, ne peut exclure les LIHG » (ASC-H) et « frottis de bas grade

histologique qui contiennent de temps à autre des cellules semblant indiquer la présence de LIHG » (LSIL-H). En Alberta, les femmes qui présentent des ASC-H sont orientées vers des services de colposcopie et celles qui présentent des LIHG sont prises en charge au moyen de frottis de Pap de suivi. Les LSIL-H ne font pas partie de la classification Bethesda et n'ont pas été définis en ce qui concerne les caractéristiques cytologiques, le signalement, la prise en charge et l'évolution clinique.

Méthodes : Tous les frottis de Pap ASC-H (n = 153) et LSIL-H (n = 189) consignés dans le système régional de renseignements de laboratoire entre décembre 2000 et décembre 2001 ont été identifiés. Toutes les données histologiques disponibles pour chacune des patientes associées au cours des deux années suivantes ont été analysées, afin de déterminer si la présence d'une lésion de haut grade histologique avait été confirmée par biopsie, technique d'excision électrochirurgicale à l'anse (LEEP) ou prélèvement à la suite d'une hystérectomie.

Résultats : Une lésion malpighienne intra-épithéliale de haut grade histologique a été identifiée chez 48 % des femmes du groupe ASC-H et 40 % des femmes du groupe LSIL-H ($P = 0,136$). Dans la plupart des cas, l'histopathologie LIHG a été déterminée au cours de la première consultation en colposcopie, ce qui semble indiquer qu'une dysplasie de haut grade histologique pourrait avoir été présente au moment du frottis de Pap d'origine.

Conclusions : Les résultats de frottis de Pap ASC-H et LSIL-H prédisent la présence d'une lésion malpighienne intra-épithéliale de haut grade histologique selon un degré de précision semblable. Puisque environ 40 % des patientes qui obtiennent un frottis de Pap LSIL-H présentent une pathologie cervicale de haut grade histologique concomitante ou subséquente, nous recommandons également l'orientation immédiate de ce groupe de patientes vers des services de colposcopie.

J Obstet Gynaecol Can 2006;28(10):884-887

INTRODUCTION

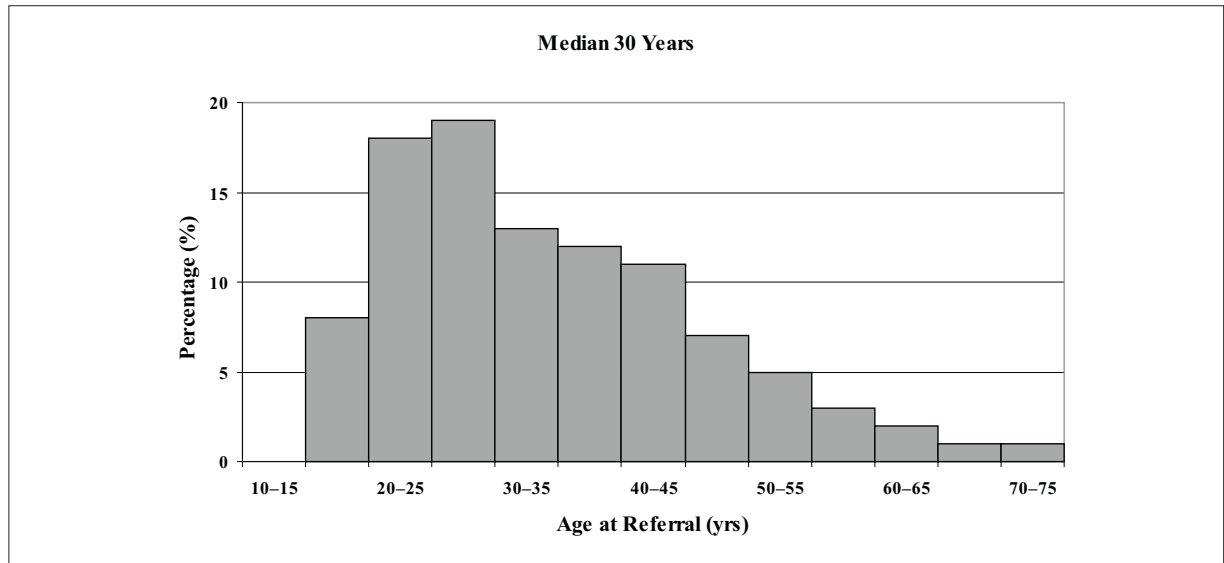
Low-grade squamous intraepithelial lesions of the cervix (LSIL) are now generally believed to be caused by a self-limiting infection of the human papilloma virus.¹ Regression rates in young women are as high as 90% over a three-year period.² The goal of current cervical screening

Key Words: LSIL cannot exclude high-grade, ASC-H, colposcopy, management, Bethesda

Competing Interests: None declared.

Received on March 29, 2006

Accepted on May 31, 2006

Figure 1. Age at Referral

programs is to identify high-grade lesions and intervene before progression to cancer.

A finding of atypical squamous cells cannot exclude HSIL (ASC-H) predicts a high-grade squamous intraepithelial lesion (HSIL) on biopsy in 50% to 60% of cases, and it therefore mandates colposcopic assessment and possible cervical biopsies.^{3,4} The designation "low-grade squamous intraepithelial lesions with occasional high-grade cells" (coined LSIL-H in this chart review) is not recognized as a Pap smear category within the revised 2001 Bethesda reporting system.⁵ These Pap smear findings have not been characterized in terms of cytological features and reporting, management, and clinical outcome. Sherman et al. described smears graded as LSIL-H as those that may manifest some or all of the following features: one HSIL cell, one or more cells with a markedly increased nuclear to cytoplasmic ratio, parakeratotic cells with enlarged irregular nuclei, squamous cells with giant nuclei, and multinucleated squamous cells.⁶ Sherman also described LSIL-H smears as those demonstrating koilocytosis or having a nucleus three times the size of an intermediate cell nucleus.

There is a paucity of published information on how well a finding of LSIL-H cytology predicts HSIL on subsequent histological examination. Nasser et al. followed 144 women with a Pap smear diagnosis of LSIL-cannot exclude HSIL. Within this group, they included the extensively keratinized squamous intraepithelial lesion that lacks definitive, nonkeratinized HSIL cells. They also included the LSIL Pap that contains rare atypical cells that are suggestive but not diagnostic of HSIL. HSIL was demonstrated on cervical biopsies in 29% of cases.⁷ Kir et al. reviewed slides with cytology described as LSIL with ASC-H, which typically

contained LSIL and only a few cells with features suggestive of HSIL; eight of 13 cases (61%) were shown to have HSIL histology.⁸ More recently, Elsheikh et al. reviewed 194 cases of LSIL-H cytology (described as ASC-H changes in a background of unequivocal LSIL), and demonstrated HSIL histology in 40.7% of cases, compared with 44.6% in a similar ASC-H cytology cohort.⁹ Elsheikh and colleagues suggested that defining LSIL-H as a separate cytologic entity would be very useful in defining prognosis because of its high predictive value for identifying HSIL-positive lesions.

Even though the number of cases in most of these reports is small, the value of LSIL-H for predicting concurrent or subsequent high-grade dysplasia is clearly demonstrated.

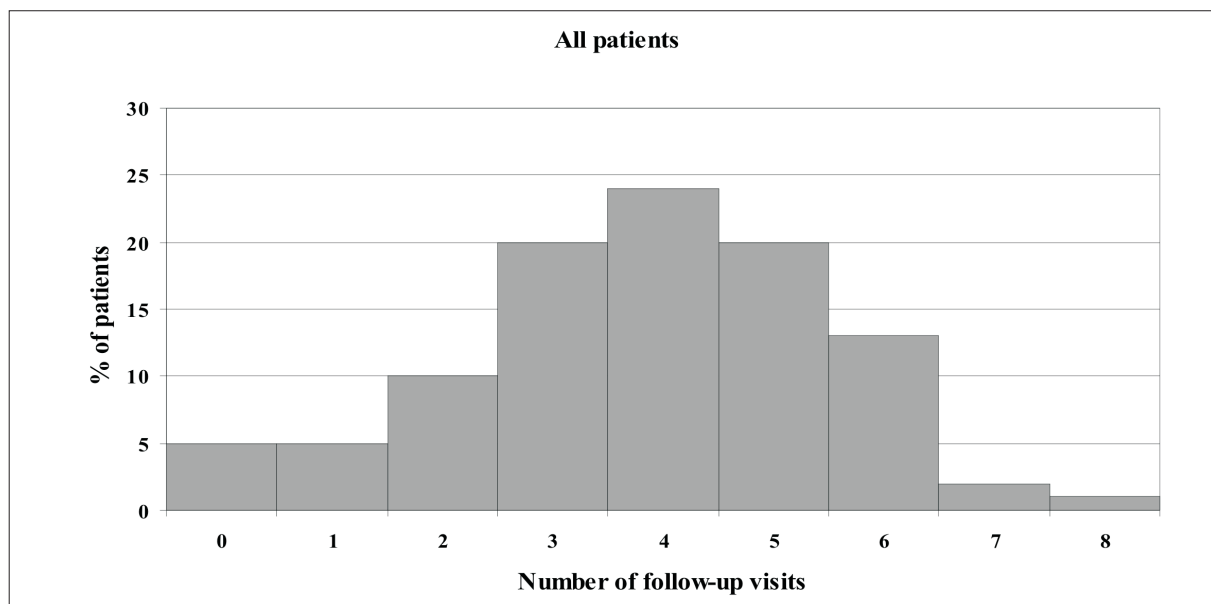
This retrospective review examines how well LSIL-H cytology in a Pap smear predicts a histological finding of high-grade dysplasia and compares clinical outcomes in women with LSIL-H cytology with outcomes in a similar group of women with ASC-H cytology.

METHODS

Women whose cytology on Pap smear showed ASC-H and LSIL-H cytology were identified using the Calgary Laboratory Information System database. We reviewed their medical records retrospectively to collect demographic information and pathologic details, including age at presentation, number of visits, and diagnostic procedures performed.

Between December 2000 and December 2001, Pap smears reported as either atypical squamous cells of undetermined significance (ASCUS) (n = 1938) or LSIL (n = 2076) were reviewed. From the ASCUS cohort, 153 ASC-H smears were identified (7.9%), and from the LSIL cohort 189

Figure 2. Number of colposcopic follow-up visits



LSIL-H smears were identified (9.1%). For each patient, all histology results were reviewed over the subsequent two-year period to determine if a high-grade lesion was ever confirmed on biopsy, loop electrosurgical excision procedure (LEEP), cone biopsy, or hysterectomy specimen. Eleven cytopathologists in Calgary were involved in assigning a diagnosis of ASC-H or LSIL-H. LSIL-H was diagnosed using the Sherman criteria, as described above. As directed by local guidelines, all of these patients were referred for colposcopy.

Analysis was performed using the STATA statistical software (Release 8.2, College Station, TX). We used 80% power to detect a 10% difference between ASC-H and LSIL-H in predicting subsequent HSIL on histopathology. Chi-square test of proportions was used in the analysis. Ethics approval was provided by the Conjoint Health Research Ethics Board, University of Calgary.

RESULTS

The median age of women at the time of the initial Pap smear requiring referral was 30.5 years, and almost one half of the women were aged between 24 and 41 years (Figure 1). There was no significant age difference between the women in the ASC-H group and those in the LSIL-H group. Over the two-year follow-up period, most women had four visits; very few women had more than six visits (Figure 2). Cervical biopsy was by far the most common tissue sampling technique. The cervical biopsy detected HSIL at the first colposcopic assessment in 89% of cases. The majority of first assessments were within three months of the referral Pap smear indicating a need for colposcopy. Of

Positive predictive value of ASC-H and LSIL cytology in predicting HSIL histology

Cytologic Abnormality	HSIL Diagnosis, <i>P</i> = 0.136		Total
	No	Yes	
ASC-H	80 52.29%	73 47.71%	153 100%
LSIL-H	114 60.32%	75 39.68%	189 100%
Total	194 56.73%	148 43.27%	342 100%

note, 13% of women with ASC-H cytology and 15% of women with LSIL-H cytology did not have any biopsies performed. Of the 146 LEEP biopsies performed in the two groups of women, 81% had histologically proven HSIL. As shown in the Table, 48% of women with ASC-H cytology on referral had HSIL subsequently confirmed on histopathology, compared with 40% of women with LSIL-H cytology (*P* = 0.136). One squamous cell cancer was identified in each cytology group.

DISCUSSION

The findings in this retrospective review underscore the importance of judicious follow-up of any Pap smear showing LSIL with a descriptive qualifier suggesting high-grade

cells. It appears that even occasional high-grade cells on cytology are highly predictive of finding HSIL on histology. The rates of a subsequent HSIL lesion are not statistically different in women referred because of Pap smears showing ASC-H or LSIL-H cytology. Standard Canadian practice dictates referral for colposcopy in women with ASC-H cytology on Pap smear. However, there is no standard reporting system for cytopathologists who identify a few high-grade cells on a Pap showing LSIL. Similarly, there are no management guidelines for family practitioners or gynaecologists who receive an LSIL-H cytology report. Undoubtedly, practice patterns vary greatly between provinces. We recommend that management of LSIL-H and ASC-H Pap smears be the same, because there is no statistical difference in their ability to predict high-grade histopathology. If women whose Pap smears showing LSIL-H are not referred for colposcopy, 40% of these patients will have undiagnosed high-grade dysplasia.

The fact that 89% of all patients who eventually had a histologic diagnosis of HSIL had tissue confirmation on the first colposcopic visit suggests that HSIL was present at the time of the Pap smear that generated the referral. This gives further credence to managing these patients with immediate colposcopy.

Eighty-one percent of LEEP cone biopsies in this review confirmed the presence of an HSIL lesion, suggesting that the management by the treating colposcopist was appropriate. Of concern, however, is the proportion of these moderately high-risk patients who had no tissue biopsies within the two-year period examined (15% of women with ASC-H and 13% of those with LSIL-H). These patients would be at increased risk of eventually developing cervical cancer if they were lost to follow-up indefinitely.

Our findings are similar to those in the largest and most recently reported study, by Elsheikh et al., which reports a Pap smear with LSIL-H having a 40% chance of predicting a high-grade dysplasia.⁹

CONCLUSIONS

LSIL-H cytology is highly predictive of high-grade cervical dysplasia, and women with this cytology must be referred for colposcopy. It is most helpful for pathologists to comment on such cytological abnormalities, even if this description is outside the current Bethesda nomenclature.

ACKNOWLEDGEMENTS

We'd like to thank Dr Karen Kopciuk and Mr Thomas Speidel for their statistical assistance.

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