Journal of the American Society of Cytopathology (2015) 4, 225–231

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jascyto.org/

ORIGINAL ARTICLE

HPV testing results and histologic follow-up in women with ASC-H cytology in different age groups

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Received 30 November 2014; received in revised form 9 January 2015; accepted 13 January 2015

KEYWORDS
Cervical cytology;
ASC-H;
HPV testing;
CIN2+;
Age groups

Introduction Assessment on human papillomavirus (HPV) testing and disease outcome of atypical squamous cell, cannot exclude high grade squamous intraepithelial lesion (ASC-H) in different age groups is limited in published reports. We reviewed our experience over a 5-year period on ASC-H cytology and correlated age distribution with high-risk HPV (HR-HPV) status and histological follow-up in a large cohort study.

Materials and methods Women with ASC-H cytology were retrieved from the hospital database. HR-HPV status and histological diagnoses on cervical biopsy or loop electrosurgical excisional procedure specimens were reviewed and correlated to 5 age groups.

Results Ages of women with ASC-H ranged from 16 to 88 years, with 42% women <30 years and 58% women >30 years. Among 647 cases diagnosed as ASC-H, 96% (618) had HR-HPV testing results, including 68.2% HR-HPV positive and 31.8% HR-HPV negative. HR-HPV positivity of ASC-H gradually decreased from 95.2% in women <20 years to 40.6% in the age group >51 years. Histologic follow-ups were available for review in 80% (517) of the cases. Cervical intraepithelial neoplasia, grade 2 or higher (CIN2+) lesions were found in 40.3% (208) cases, including 92.9% women with HR-HPV-positive/ASC-H and 7.1% of women with HR-HPV-negative/ASC-H. The detection rate of CIN2+ by ASC-H gradually decreased from 51.2% in women <20 years to 18.2% in women >51 years. The majority of postmenopausal women with HR-HPV-negative/ASC-H had atrophy-related change.

Conclusions The specificity of ASC-H cytology in detection of cervical CIN2+ lesions is age-dependent: higher in younger women <30 years, but gradually decreased in women >30 years. The vast majority

Drs. Chen and Baker contributed equally in this study.

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http://dx.doi.org/10.1016/j.jasc.2015.01.005

(93%) of CIN2+ lesions were seen women with HR-HPV-positive/ASC-H. HR-HPV testing improves the accuracy and specificity in women with ASC-H in almost all age groups, especially in age groups older than 40 years.

Introduction

According to the Bethesda System to report cervical cytology,[1] the atypical squamous cell (ASC) category was subdivided into 2 categories: 1) ASC of undetermined significance (ASC-US), and 2) ASC, cannot exclude high-grade squamous intraepithelial lesion (ASC-H). In 2012, the American Society for Colposcopy and Cervical Pathology revised its 2006 guidelines for management of women with cytologically abnormal cervical cancer screening tests.[2,3] The recommended treatment for women diagnosed with ASC-H, however, remained the same (referral to colposcopy). If the histological diagnosis is less severe than CIN2-3, the patient should return for repeat cytology or HPV DNA testing. Colposcopy is recommended if repeat cytology is ASC-US or greater or repeat human papillomavirus (HPV) DNA test is positive. Although the guidelines acknowledged the need to treat special populations of women with ASC-US differently (eg, adolescent, pregnant, or postmenopausal), they recommended treating all women with a cytologic diagnosis of ASC-H in the uniform manner described in this paragraph.[2]

Numerous studies have examined clinical significance and histological follow-up of ASC-H patients.[4-10] The ALTS (Atypical Squamous cells of Undetermined Significance/Low Grade Squamous Intraepithelial Lesion Triage) study has shown that age is an important factor in disease outcome and application of reflex HR-HPV DNA testing for ASC-US cytology.[5] However, assessment of the impact of age distribution on disease outcome and on HR-HPV status of ASC-H is limited due to the small number of cases in the previously published studies. Taking advantage of being a hospital that instituted a policy as early as 2003 in applying reflex HR-HPV testing on most, if not all, of ASC-H among those women <30 years and applying concurrent HR-HPV testing on all women older than 30 years regardless of cytologic diagnosis, we have retrospectively reviewed our experience of ASC-H diagnosis. The purpose of this large retrospective study was to assess the impact of age on both the histological outcome and HPV status of ASC-H Papanicolaou (Pap) tests. In addition, we hoped to offer suggestions to clinical management guidelines on ASC-H based on different age groups.

Materials and methods

This retrospective study was approved by the Institutional Review Board of the Cleveland Clinic. All ThinPrep (Hologic, Marlborough, Mass) cases with a diagnosis of ASC-H from February 1, 2005 to December 31, 2010 were retrieved from the pathology database of the Cleveland Clinic by performing an electronic search. Duplicate cases were removed from the study. Patients with concurrent diagnosis of both low-grade squamous intraepithelial lesion and ASC-H or atypical glandular cells and ASC-H were also excluded from the study. Follow-up data and HR-HPV status were gathered using the patients' electronic medical records.

HPV testing was performed by the Hybrid Capture 2 HR-HVP DNA test (Digene, Gaithersburg, Md). This test detects 13 HR-HPV types, including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. All available follow-up histologic diagnoses from cervical biopsies, endocervical curettages, loop electrosurgical excisional procedure, conization procedures, and hysterectomies were gathered using hospital electronic medical records and a pathology database. Patients underwent a range of 1 to 5 biopsies after cytologic tests during follow-up. The most severe histological diagnosis was recorded if multiple biopsies were performed. For the purposes of this study, histological diagnoses of CIN2, CIN2-3, CIN3, endocervical adenocarcinoma in situ, and invasive squamous cell carcinoma were grouped as CIN2+. The patients' HR-HPV statuses within 6 months of the initial cytologic test were recorded.

The sensitivity, specificity, positive predictive value, and negative predictive value for reflex HPV DNA testing for the detection of clinically significant squamous lesions (CIN2+) among women with ASC-H were calculated. Statistical comparisons were performed using the chi-square test or Fisher exact test if a group had <5 cases with a level of <0.01 defined as statistically significant. Calculations were performed with the SAS system (Cary, NC).

Results

ASC-H rate and cytologic criteria

The cytomorphologic criteria used by our institution in diagnosing ASC-H strictly follow the 2001 Bethesda System. ASC-H diagnosis was rendered when a few ASCs with higher nuclear/cytoplasmic ratio and nuclear atypia were present, but the quantity is short of making diagnosis of high-grade squamous intraepithelial lesion (HSIL). Of a total 302,363 Pap tests performed at our institution over a 5-year period, overall abnormal cytology is at 12.7%. Among them, 647 women were cytologically diagnosed with ASC-H. The rate in diagnosing of ASC-H is approximately 0.2%, which is equivalent to the rate of atypical glandular cells diagnosis (0.19%), but less than the HSIL rate (0.4%), and much less than the ASC-US rate (8%) in our institution.