A prospective study of risk-based colposcopy demonstrates improved detection of cervical precancers

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BACKGROUND: Sensitivity for detection of precancers at colposcopy and reassurance provided by a negative colposcopy are in need of systematic study and improvement.

OBJECTIVE: We sought to evaluate whether selecting the appropriate women for multiple targeted cervical biopsies based on screening cytology, human papillomavirus testing, and colposcopic impression could improve accuracy and efficiency of cervical precancer detection.

STUDY DESIGN: In all, 690 women aged 18-67 years referred to colposcopy subsequent to abnormal cervical cancer screening results were included in the study (ClinicalTrials.gov: NCT00339989). Up to 4 cervical biopsies were taken during colposcopy to evaluate the incremental benefit of multiple biopsies. Cervical cytology, human papillomavirus genotyping, and colposcopic impression were used to establish up to 24 different risk strata. Outcomes for the primary analysis were cervical precancers, which included p16‡ cervical intraepithelial neoplasia 2 and all cervical intraepithelial neoplasia 3 that were detected by colposcopy-guided biopsy during the colposcopy visit. Later outcomes in women without cervical intraepithelial neoplasia 2‡ at baseline were abstracted from electronic medical records.

RESULTS: The risk of detecting precancer ranged from 2-82% across 24 strata based on colposcopy impression, cytology, and human papillomavirus genotyping. The risk of precancer in the lowest stratum increased only marginally with multiple biopsies. Women in the highest-risk strata had risks of precancer consistent with immediate treatment. In other risk strata, multiple biopsies substantially improved detection of cervical precancer. Among 361 women with cervical intraepithelial neoplasia <2 at baseline, 195 (54%) had follow-up cytology or histology data with a median follow-up time of 508 days. Lack of detection of precancer at initial colposcopy that included multiple biopsies predicted low risk of precancer during follow-up.

CONCLUSION: Risk assessment at the colposcopy visit makes identification of cervical precancers more effective and efficient. Not finding precancer after a multiple-biopsy protocol provides high reassurance and allows releasing women back to regular screening.

Key words: biopsy, cervical cancer screening, colposcopy, precancer, risk

Introduction

Cervical cancer screening programs rely primarily on detection and removal of cervical precancers before they progress to invasive cancers. In most high-resource settings, referral to colposcopy with biopsy is prompted by positive primary screening.1,2 The colposcopic evaluation with colposcopic biopsies is critical to decide about returning women to routine screening, more intensive surveillance, or treatment. Taking a single biopsy from the most concerning area on the cervical transformation zone misses a substantial proportion of precancers.3,5 Taking multiple targeted biopsies during colposcopy improves detection of prevalent precancers,4 a practice that was recommended in recent colposcopy guidelines.6 The routine use of 4-quadrant random biopsies for detection of precancer remains controversial.4,9

Apart from substantial variability of colposcopy practice, colposcopy populations differ in referral criteria and hence the underlying population risks of cervical precancer. Within a colposcopy population, women present with different absolute risks of cervical precancer based on their screening cytology and human papillomavirus (HPV) test results. This information could be used to improve detection of cervical precancers, according to the principle of precision prevention.10 However, currently, results from cytology or HPV tests are not systematically used to modify colposcopy practice.

Because of limited sensitivity of colposcopy-biopsy procedures, the reassurance from a negative colposcopy result can be low. Women without precancer detected at colposcopy often undergo repeated colposcopy procedures for an extended period of time until they are released back to regular screening.

The Biopsy Study previously showed the incremental benefit of multiple lesion-directed colposcopic biopsies.6 Here, we evaluated whether selecting the appropriate women for multiple targeted cervical biopsies based on screening cytology, HPV testing, and colposcopic impression could improve accuracy and efficiency of cervical precancer detection. Furthermore, we studied outcomes following a negative colposcopy to evaluate the reassurance provided by negative colposcopy.

Materials and Methods

Population

The Biopsy Study included women age ≥18 years with abnormal cervical cancer screening results referred to colposcopy.
at the University of Oklahoma Health Sciences Center (OUHSC) from February 2009 through August 2011, as previously described. Among 1373 eligible women, 690 (50.3%) agreed to participate in the study. Written informed consent was obtained from all women enrolled and institutional review board approval was provided by OUHSC and the US National Cancer Institute.

Colposcopy and biopsy protocol, histologic endpoints, cytology, and HPV testing

Colposcopies were performed by experienced attendings and clinical fellows of the OUHSC colposcopy clinic. Six colposcopists performed between 60-179 colposcopic examinations each. The following grades of colposcopic impression were distinguished, based on the listed features: high-grade colposcopy impression (rapidly appearing and slowly fading, thick acetowhitening; coarse mosaicism and coarse punctuation; sharp border, inner border sign, ridge sign, peeling edges; flat contour); low-grade colposcopy impression (thin and rapidly fading acetowhitening; fine mosaicism and fine punctuation; irregular border; raised contour); acetowhitrning (acetowhitrning, but none of the features listed for high- or low-grade impression); normal (no acetowhitrning and none of the features listed for high- or low-grade impression). Up to 4 directed biopsies were taken from distinct areas of epithelium that turned white on the application of 5% acetic acid in the cervical transformation zone or large heterogeneous lesions extending over multiple quadrants (lesion-directed biopsies). If <4 lesion-directed biopsies were taken, a nontargeted biopsy was added at the transformation zone in a quadrant without acetowhite lesions. All biopsies were ranked by order of severity by the colposcopist and each biopsy specimen was evaluated separately in histology. An adjacent section was stained for p16 using the CINtec® p16 histology assay (Roche mtm Laboratories, Mannheim, Germany) and evaluated as previously described. We adopted the lower anogenital squamous terminology guidelines for this analysis: all cervical intraepithelial neoplasia (CIN)2 cases that stained diffusely positive for p16 were included as high-grade squamous intraepithelial lesion (HSIL) histology, along with all CIN3 cases regardless of p16 staining. Only 10% of 197 CIN2 were p16−, inclusion of which did not affect risk strata and disease yield in a meaningful way.

In this population, endocervical sampling detected very little disease beyond cervical biopsies and was not considered for histologic endpoints. Referral cytology was community-based and included conventional smears and liquid-based cytology, using the Bethesda nomenclature with the categories: atypical squamous cells of undetermined significance (ASC-US); low-grade squamous intraepithelial lesion (LSIL); atypical squamous cells, HSIL cannot be excluded; HSIL; and atypical glandular cells. Women with normal for intraepithelial lesion or malignancy cytology results were not referred to colposcopy. During colposcopy, a cervical specimen was collected using a broom device and transferred to PreservCyt solution (Hologic, Marlborough, MA) for HPV DNA analysis. HPV detection and genotyping were based on linear array HPV genotyping test (Roche Molecular Diagnostics, Branchburg, NJ), as previously described.

Statistical analysis

The strata in this analysis were defined based on the risk measures that strongly predicted yield of cervical precancer in our previous analysis. The population was stratified into 24 subgroups based on colposcopy impression (high-grade; low-grade; acetowhitrning; normal), referral cytology (HSIL, including atypical squamous cells, HSIL cannot be excluded and atypical glandular cells; LSIL; ASC-US), and HPV16 status (positive; negative). We did not include age strata because age was not associated with yield of precancer in our population. A total of 647 women had information on all 3 risk measures and histologic endpoints. For each stratum, the absolute risk of HSIL histology was calculated by dividing the number of HSIL endpoints over all women in the stratum. Similar strata were formed for combinations of colposcopy impression and referral cytology alone (12 strata, n = 650 women), as well as combinations of colposcopy impression and HPV16 status alone (8 strata, n = 673 women). For subsequent analyses, we collapsed into 12 strata using 2 cytology categories (HSIL vs <HSIL), 2 HPV categories (HPV16+/HPV16−), and 3 colposcopy impression categories (high-grade, low-grade, acetowhitrning/normal). Three strata with ≤12 women (ie, acetowhitrning or normal impression/<HSIL/HPV16+ with 11 women; acetowhitrning or normal impression/HSIL/HPV16− with 12 women; and
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