Clinical Factors That Predict Discrepancy between Cervical Cytology and Colposcopically Directed Biopsies

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Abstract—

Objective: The aim of this study was to identify clinical variables that might account for the discrepant results between cervical cytology (CC) and corresponding colposcopically directed cervical biopsy (CB).

Methods: The pathology database was reviewed for consecutive cases of cytology and their corresponding biopsies between 2010 and 2012. 114 discordant cases and 190 concordant cases (control group) were identified. Discrepant cases were classified as (1) major and (2) minor. A major discrepancy is a case with high-grade cytology (ASC-H or HSIL) and histologic benign or CIN 1. A minor discrepancy is a case with low-grade cytology (ASC-US or LSIL) and histologic CIN-2 or -3. Uni- and multivariate analyses were performed to identify clinical variables associated with CC/CB discrepancy.

Results: The mean age for patients was 41 (range 14-73). Of the total study population, 57% were Hispanic, 24% were white and 19% identified with another racial group. Major discrepancies were 4 times more likely to occur among CC collected by mid-level practitioners compared to CC collected by physicians (p=0.037). Major discrepancies were also found to be associated with benign or CIN 1 on clinical impression at colposcopy (p=0.036). Furthermore, an immune compromised status showed a trend towards significance for major discrepancies (p=0.062). High-risk HPV positivity was associated with a 3.5 fold increase in observing a minor discrepancy between CC and CB (p=0.008). Minor discrepancy was also associated with younger age of patient (p = 0.001). The training level of the colposcopist did not significantly impact the rate of CC/CB discrepancy.

Conclusions: This study identifies several variables associated with CC/CB discrepancies that are important for a rigorous multi-disciplinary quality assurance effort.

Keywords — Cervical cytology; cervical biopsy; discrepancy

INTRODUCTION

Cervical cytology, along with high-risk human papillomavirus (HPV) testing, is the standard screening modality for cervical dysplasia and malignancy. Patients with abnormal cervical cytology are triaged based on the American Society for Colposcopy and Cervical Pathology (ASCCP) consensus guidelines¹. Abnormal cytologic results are often followed with a colposcopic exam and tissue biopsy.

Low-grade cytologic abnormalities include “atypical squamous cells of unknown significance” (ASCUS) and “low grade squamous intraepithelial lesions” (LSIL). Low-grade abnormalities are most often correlated with a benign or low-grade (CIN 1) histologic diagnosis. High-grade cytologic abnormalities include “atypical squamous cells of unknown significance – can not rule out high grade” (ASC-H) and “high grade squamous intraepithelial lesions” (HSIL) and reflect a high-grade histologic diagnosis (CIN 2 or 3) in 90% of cases⁵-⁶. Disagreement between cytology and histology represents a significant dilemma for clinicians and pathologic laboratories. A consensus review conference amongst pathologists and cytotechnologists can often resolve the discrepancy, but it is not uncommon for the discrepancy to remain even after review among experienced staff⁹.

Sampling error during colposcopy is considered a major contributor to discrepancy between CC and CB. Hearp et al. reported that among patients with a HSIL CC followed by a low-grade CB (CIN 1 or less), 56% later went on to have CIN 2/3 on subsequent biopsies (either repeat CB or diagnostic excisional procedure)⁷. The utility of deep sectioning of CB specimens to reduce the rate of discrepancy has been studied, with conflicting results ⁶-⁷. Similarly, the usefulness of endocervical curettage to increase the quantity of tissue sampled and decrease the discrepancy rate is controversial⁸.

The aim of this study is to identify clinical variables that might account for the discrepant results between cervical cytology (CC) and corresponding biopsy (CB).

MATERIALS AND METHODS

After obtaining IRB (Institutional Review Board) approval, the archives of the cytopathology and surgical pathology
databases at the Los Angeles County + University of Southern California Medical Center (LAC+USC) were searched over a 2 year period (2010-2012) for consecutive cases of CC with the corresponding CB. The clinical data such as patient demographics, gynecologic history, Human papilloma virus (HPV) and immunodeficiency status, CC and CB locations, training level of those collecting CC and CB, time interval between CC and CB and clinical impression at the time of colposcopy, were all retrieved from the electronic medical record (Table 1).

Subjects were divided based on the CC results into 2 groups; high-grade cytology, defined as ASC-H or HSIL, and low-grade cytology defined as ASCUS or LSIL. Within the high-grade cytology group, discordancy was labeled “major” and defined as benign or low-grade cervical intraepithelial neoplasia (CIN 1) on CB. Within the low-grade cytology group, discordancy was labeled minor and defined as high-grade dysplasia (CIN 2/3) on CB.

Clinical variables were tested for association with CC/CB discrepancy. Due to the limited sample size, univariate analysis was used as a screening tool for potential predictor variables. Fisher’s exact test was used for categorical variables and odds ratio (OR) was reported. For continuous variables, logistic regression was used and exp(β) was reported, where β is the coefficient in the logistic regression. Multivariate logistic regression was used to fit the significant variables found in the univariate analysis (p<0.05). In particular, the exact logistic regression was used for multivariate test involving categories with zero count. For the multivariate model, we report the count R2, which is essentially the probability of correct predicted values.

RESULTS

Three hundred four patients were included in this study, where 190/304 (62.5%) patients had concordant results and 114/304 (37.5%) of patients had discordant results.

Within the high-grade cytology group, 16 cases were concordant and 89 were discordant. The clinical data is summarized in Table 2. In univariate analysis, training level of the CC performer and the clinical impression at the time of colposcopy showed significant association with the outcome (discrepancy between CC and CB). Meaning, when a non-MD practitioner performs the CC it is 4 times more likely to show discrepant results on the CB (p=0.123). Meanwhile, clinical impression of benign or CIN 1 at colposcopy is much more likely to have discrepant results than an impression of CIN 2 or 3 (p = 0.011). Both factors retain statistical significance in the multivariate test (p = 0.037 and 0.036, respectively) with count R2 = 0.85. Being immune compromised showed a tendency to be a predictive factor for discrepancy in the univariate analysis (p=0.062) but did not reach a statistically significant p value.

Within the low-grade cytology group, 174 cases were concordant and 25 were discordant. The clinical data is summarized in Table 3. Univariate analysis showed that HPV status had a strong association with discrepant results (p=0.006). Meaning patients with high-risk HPV positivity are 3.5 times more likely to have discrepant results in comparison to HPV negative or unknown patients. Age is also a significant factor (exp(β) = 0.936, p = 0.002). Exp(β) less than 1 suggests younger age is associated with higher chance of discrepant results. In multivariate analysis, both HPV and age are still significant (p = 0.008 and 0.001, respectively), with a count R2 = 0.87. Additionally, gravidity and parity show an association (p = 0.012 and 0.041, respectively) in the univariate test. However they do not retain statistical significance in the multivariate test (p = 0.394 and 0.124, respectively). The colposcopist making a clinical impression of CIN 2/3 had a tendency to have an association with discordant results in univariate analysis (p=0.092).

DISCUSSION

The implications of discrepant cervical cytology and histology results are far-reaching. If cervical biopsy results following HSIL or ASC-H cytology are not CIN 2/3, ASCCP consensus guidelines allow three options: co-testing at 12 months, pathology review or diagnostic excisional procedure. Repeat testing in one year risks progression of a high-grade dysplastic lesion6, while an excisional procedure includes significant risks, including an increased rate of second trimester loss in subsequent pregnancies7. This scenario is challenging for both physicians and patients alike. Likewise, a high-grade abnormality on CB following CC resulted as ASCUS or LSIL represents a significant disagreement between cytology and histology and in some cases a potential “near miss” (one option for follow-up of ASCUS CC is to defer colposcopy and repeat cytology in 12 months).

The clinical significance of the association between CC/CB discrepancy among high-grade cytologic abnormalities and having the cervical cytology collected by a non-MD practitioner is unclear. One possible explanation for this association is that at our medical center, physicians tend to see patients with known gynecologic problems (including prior abnormal CC), while mid-level providers tend to see a lower risk population. Perhaps a low risk population is more prone to “false positive” high-grade cytology, with benign or low-grade histology on biopsy, while a high-risk population is more likely to have actual histologic dysplasia after a high-grade pap smear. We did not see the same effect in either of the high-grade or low-grade cytologic groups when comparing MD versus non-MD colposcopists. This is in agreement with previous studies that have demonstrated the training level of the colposcopist does not significantly alter the accuracy of the assessment8. It is not unexpected that a clinical impression of benign or CIN 1 on colposcopy in the high-cytology group is associated with CC/CB discrepancy, as this means that the colposcopy provider is predicting a discrepancy (i.e. not grade high-grade dysplasia) based on the exam.

The causative role that HPV plays in cervical dysplasia and malignancy is well documented. High-risk HPV testing is an important part of cervical dysplasia screening, and is being
considered as a first-line screening method independent of CC\textsuperscript{11}. Among low-grade cytologic cases, HPV status was significantly associated with discordant results, meaning a high-grade histologic diagnosis was more likely with HPV positivity. This finding supports the triage role that high-risk HPV testing plays in the current ASCCP guidelines. Among the low-grade cytology group, younger was also associated with discrepancy.

Several other potential clinical factors were examined but did not reach statistical significance. Prior research has suggested a prolonged time interval between CC and CB can contribute to discordant results, but this effect was not seen in our analysis\textsuperscript{11}. It is well documented that women with a compromised immune system secondary to human immunodeficiency virus (HIV) are at increased risk of cervical dysplasia\textsuperscript{11}. We compared rates of discordance among women with comorbidities that cause immune dysfunction, including HIV, diabetes mellitus, rheumatoid arthritis and systemic lupus erythematosus. Immune compromised status approached statistical significance as a contributor to discrepant results in the high-grade cytology group.

Our study identifies four clinical risk factors for CC/CB discrepancy. Given the relatively straightforward procedure for CC specimen collection, the clinical significance of our finding that non-MD collected cytology is a risk factor for discrepancy is unclear. It does, however, highlight the importance of consistent technique among all gynecologic providers for CC collection and colposcopic directed biopsies. Our finding that high-risk HPV positivity confers a risk for CIN 2/3 on CB in a patient with an otherwise low-grade CC is in agreement with current ASCCP guidelines that recommend use of high-risk HPV status to triage patients to surveillance versus colposcopy\textsuperscript{11}.

REFERENCES

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