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ORIGINAL ARTICLE

Significance of cytopathologist's review of Pap tests screened as negative for intraepithelial lesion or malignancy that are positive for high-risk human papillomavirus

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Introduction Cytopathologist's review of Papanicolaou tests (PTs) screened by cytotechnologists as negative for intraepithelial lesion or malignancy (NILM) that are positive for high-risk human papillomavirus (hrHPV+) may be a useful quality control measure.

Materials and methods From January 1, 2012 to December 31, 2012 all NILM/hrHPV+ PTs underwent cytopathologist's review before report issuance as per routine quality control procedures. HrHPV status was known at the time of screening and at final review. The rate of upgraded diagnoses resulting from the cytopathologist's review were examined. Two-year follow-up was obtained.

Results Cytopathologist's review upgraded 250 of 1282 PTs (19.5%) by 1 step to atypical squamous cells of undetermined significance and 13 (1%) were upgraded by 2 steps or more to low-grade squamous intraepithelial lesion or higher. During the same period, significantly fewer NILM PTs (of unknown hrHPV status) were upgraded by 2 steps or more as a result of random 10% rescreening by cytotechnologists (0.2%, $P < 0.001$). Follow-up was available in 740 of 1282 patients (57.7%). The upgraded group was significantly more likely to be referred for colposcopy (68.3% versus 30.5%, $P < 0.001$) and cervical intraepithelial neoplasia (CIN) 2 or higher (CIN2+) was diagnosed in more upgraded patients (8.9% versus 3.0%, $P < 0.01$) than in those not upgraded. There was no significant difference in the percentage of colposcopy patients diagnosed with CIN2+ in the 2 groups, respectively (13.1% versus 9.8%, $P = 0.47$).

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Conclusions cytopathologist's review of NILM/hrHPV+ PTs identified more 2-step discrepancies than routine 10% rescreening. Significantly more patients in the upgraded group were found to harbor CIN2+; however, this could be related to the higher rate of referral to colposcopy in this group.

Introduction

Quality assurance/quality control (QA/QC) programs are essential components of the functioning of a pathology laboratory. Among these, Papanicolaou (Pap) test (PT) QA/QC is among the most important and most closely regulated. The Clinical Laboratory Improvement Amendments of 1988 were written to improve quality in all laboratory testing situations and included several QA/QC specifications for Pap testing.[1][(42CFR493.1274(c)(1)] One of these recommendations is that laboratories should, at a minimum, rescreen at least 10% of PTs reported as negative for intraepithelial lesion or malignancy (NILM) by their cytotechnologists prior to report issuance. The purpose of this QC measure is to provide laboratories with a methodology of assessing individual cytotechnologist performance, reduce discrepancies, and provide optimal patient care by allowing for the detection of potential false negatives. Since the implementation of Clinical Laboratory Improvement Amendments of 1988guidelines, numerous advances have occurred in Pap testing including implementation of routine high-risk human papillomavirus (hrHPV) testing. PTs that are to be part of the 10% rescreen are chosen at random from the current case load with respect to potentially high-risk populations from clinical data available to the laboratory. However, this raises valid concerns as to whether this random subset of PTs is the most ideal and effective group from which false negative results could be detected.[2,3] Various studies have focused on measures other than the traditional 10% rescreen such as 100% rapid rescreening, rapid prescreening, or focused rescreening based on clinical risk assessment.[2-6] However, these alternate strategies have not yet been widely adopted in laboratories in the United States.

Recent screening strategies have recommended that women over 30 years be cotested with a PT and hrHPV test. Current American Society of Colposcopy and Cervical Pathology guidelines recommend lengthening the interval of screening from 3 to 5 years in women who are not at high risk for cervical cancer and have negative results from PT and hrHPV test.[7] Cotested women with NILM PTs that are positive for hrHPV (NILM/hrHPV+ PTs) have a small risk of high-grade squamous intraepithelial lesion (HSIL), and current recommendations advocate for repeat cotesting or hrHPV genotyping within 1 year.[7] A pilot study and subsequent larger scale study from the same investigators found that significantly higher 2-step discrepancies in review of NILM/hrHPV+ PTs than in randomly reviewed PTs and that focused review of NILM/hrHPV+ PTs may enhance QC.[8,9] There are no College of American Pathologists QC recommendations as to whether this group of PTs is required to be reviewed by a cytopathologist prior to report issuance.[101[42CFR493.1274(e)(1)(i)−(e)(1)(v), (e)(2)] In our laboratory, NILM/hrHPV PTs are sent for a cytopathologist's review prior to report issuance as part of routine QC, and in this study, we investigate the utility and impact of this practice.

Materials and methods

Institutional review board approval was obtained for this study. A computer search of the electronic medical record at our tertiary-care academic medical center was used to identify all consecutive PTs from January 1, 2012 to December 31, 2012 that were interpreted by cytotechnologists as NILM that were also hrHPV+ in women over 30 years of age who were cotested. Consultation PTs were excluded. These NILM/hrHPV+ PTs were sent to a cytopathologist for review prior to issuance of the final report as per our laboratory's routine QC protocol. HrHPV status was known at the time of both the initial screening by the cytotechnologist and the final review by the cytopathologist. Final cytopathologist diagnoses were recorded and compared with the initial cytotechnologist diagnosis. Proportions of cases upgraded from NILM—1 step, 2 steps, or greater—as a result of the cytopathologist's review were calculated and recorded. During the same period, the proportion of cases upgraded by 2 steps or greater as a result of routine 10% rescreening of random PTs (of unknown hrHPV status) was recorded.

For PTs in the NILM/hrHPV+ group, for 2 years, follow-up histologic studies including repeat PTs, cervical biopsies, endocervical currettings, cervical excisional biopsies (loop electrosurgical excision procedure and conization), and hysterectomy specimens were retrieved and the highest histologic lesion was recorded. Histologic outcome of cervical intraepithelial neoplasia 2 or higher (CIN2+) was calculated and compared using Fischer exact testing in the upgraded and nonupgraded groups. Cases with no follow-up of any kind were excluded from this analysis.

Cytologic preparation and molecular testing for hrHPV

All PTs were prepared into ThinPrep smears (Hologic Corporation, Boxborough, Mass) by transferring exfoliated cells into a vial containing PreservCyt fixative (Hologic) by vigorous agitation of the sampling device against the vial wall. The vials were then transported to the processing