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ORIGINAL ARTICLE

Human papillomavirus testing and cytologic/histopathologic "test of cure" follow-up results after excisional treatment for high-grade cervical intraepithelial neoplasia

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Introduction Recently published guidelines now specifically recommend cytology and HPV cotesting as follow-up after high-grade cervical intraepithelial neoplasia (CIN 2/3) excision.
Materials and methods A total of 988 patients with CIN 2/3 treated by excision between July 2005 and December 2009 were identified with available "test of cure" follow-up results over an average of 36 months. Average age was 32 years.
Results CIN 2/3 was reported during follow-up in 67 of 988 (6.8%) patients; 45 of 67 (67.2%) follow-up CIN 2/3 diagnoses were within 2 years of excision. Post-treatment CIN 2/3 was significantly more likely after initial CIN 3 grade, positive excision margins, and human papillomavirus (HPV)-positive follow-up results, but not significantly associated in this cohort with age. A total of 514 women had follow-up HPV tests, and 32.3% had at least 1 HPV-positive result. Post-treatment CIN 2/3 was diagnosed in 24 of 165 (14.5%) patients with at least 1 follow-up HPV-positive result and in 6 of 349 (1.7%) with only follow-up HPV-negative results. No HPV-negative/cytology-negative follow-up results were documented among 30 post-treatment patients later developing recurrent CIN 2/3.
Conclusions Cytology and HPV cotesting facilitates early intervention during follow-up after CIN 2/3 excision.

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Introduction

Recently updated American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines now recommend follow-up cytology and human papillomavirus (HPV) cotesting at 12 and 24 months after excisional treatment for high-grade cervical intraepithelial neoplasia (CIN 2/3).[1] This updated follow-up protocol is based primarily on recently published data from Kaiser Permanente Northern California, a large integrated health system that has since 2003 been using cotesting for routine cervical screening, management of screening abnormalities, and management of women after colposcopy and treatment of CIN 2 or more severe lesions (CIN 2+).[2] According to published Kaiser data, the lowest 5-year post-treatment risk for CIN 2+ was achieved after either 1 or 2 "double-negative" cotest results; higher 5-year post-treatment risks for CIN 2+ were documented after either 1 negative HPV result or 1 conventional Papanicolaou (Pap) test result.[2] These findings are consistent with several earlier large international reviews that also reported lowest post-treatment CIN 2+ risk after both negative cytology and HPV cotest results.[3-5] As very limited US data[6] are available apart from Kaiser's, a system that separately collects HPV test and cytology samples and which did not until 2009 begin to use liquid-based cytology, we decided to examine post-CIN 2/3 treatment "test of cure" follow-up cervical screening data from our own large integrated health system, one that since 2000 has used prevalent US Food and Drug Administration (FDA)-approved liquid-based cytology methodology and FDA-approved from-the-vial HPV testing.

Materials and methods

Patient accrual

After obtaining institutional review board approval at the University of Pittsburgh Medical Center, a retrospective study was initiated. A computer-based search of the CoPath (Cerner Corporation, Kansas City, Mo) laboratory information system database at Magee-Womens Hospital of the University of Pittsburgh Medical Center was carried out to retrieve cases with histopathologic diagnoses of CIN 2 or CIN 3 (CIN 2/3) diagnosed during a 54-month period between July 2005 to December 2009. The results of surgical pathology reports, preceding Pap tests, and preceding high-risk human papillomavirus (hrHPV) DNA tests were collected from the laboratory information system.

Cytologic methods

Cytologic testing used ThinPrep Pap tests prepared according to manufacturer's specifications from PreservCyt samples using an automated processor (ThinPrep 3000, Hologic Inc., Marlborough, Mass). Staining of slides was performed on a Sakura Tissue-Tek Automated Slide Stainer (Sakura Fintek USA Inc., Torrance, Calif). Beginning in December 2004, location-guided, computer-assisted screening of ThinPrep Pap test slides was used, employing the ThinPrep Imaging System.[7] The ThinPrep Imaging System performed analyses on batches of up to 250 ThinPrep Pap test slides with specialized imaging software. All specimens were processed and evaluated in the pathology laboratory at Magee-Womens Hospital and reported using current Bethesda System 2001 terminology.[8] In this report, all low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL) results and other current Bethesda System result terminology refer to cytologic interpretations.

Human papilloma virus DNA testing

University of Pittsburgh Medical Center system clinical providers order hrHPV DNA testing according to several ordering options as follows: reflex HPV testing following atypical squamous cell Pap test interpretations, routine HPV cotesting with Pap tests from women 30 years and older, and HPV cotesting regardless of either age or Pap test results. The hrHPV DNA detection in ThinPrep Pap test PreservCyt vial fluid was performed using the US FDA-approved Hybrid Capture 2 assay method (Qiagen Corp., Minden, Germany) that tests for hrHPV and intermediate-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.[9] The results of hrHPV DNA testing were either positive or negative, based on a threshold of 1 pg/mL HPV DNA.

Histopathologic diagnosis

All diagnoses of CIN 1 or CIN 2/3 in this study refer to histopathologic interpretations of surgical pathology specimens, including cervical biopsies, endocervical curettage specimens, and/or diagnostic excisional procedures using either loop electrosurgical excision procedures or cold knife cervical conization. Histopathologic diagnoses were rendered by subspecialized staff pathologists at Magee-Womens Hospital whose practices are largely limited to examination of gynecologic and breast pathology specimens. Cases initially diagnosed as CIN 2/3 are required to be confirmed by a second reviewing pathologist per MWH policy.[10] Immunohistochemical staining with P16 and Ki-67 is also liberally used by staff pathologists to increase the reliability of CIN 2/3 diagnoses whenever questionable histopathologic changes are identified.[11]

Statistical analysis

Pearson χ^2 test was used for statistical analysis (Fisher exact test for small sample sizes) conducted on SAS 9.1 system (SAS Institute Inc., Cary, N C). A value of $P < 0.05$ was considered statically significant.