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ORIGINAL ARTICLE

Increased cervical cancer risk associated with extended screening intervals after negative human papillomavirus test results: Bayesian risk estimates using the Pittsburgh Cervical Cancer Screening Model

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Risk assessment

Introduction Questions have recently been raised about the acceptability of increased cervical cancer risk projected with the new guideline-recommended rescreening interval of 5 years after negative cytology and human papillomavirus (HPV) cotest results. Additional data sources capable of evaluating cervical cancer risk over time are being sought. We employed the continuously updated Bayesian Pittsburgh Cervical Cancer Screening Model (PCCSM) to estimate invasive cancer risks for patients screened at extended screening intervals after negative HPV test results.

Materials and methods The analyzed database included cervical screening data collected over 10 years (2005-2014) at Magee Womens Hospital with 976,624 liquid-based cytology (LBC) results, 285,351 companion high-risk US Food and Drug Administration–approved HPV test results from LBC vials, and 112,435 follow-up histopathologic results from surgical procedures with cervical tissue sampling. Histopathologic cervical cancer risk estimates for patients with prior double negative results with cervical LBC and from-the-vial HPV cotesting were computed using the PCCSM for women rescreened at intervals ranging from 1 to 9 years. Similar risks were computed for women with any negative HPV test result, not considering cytology results.

Results Histopathologic invasive cervical cancer risk computed following LBC and HPV cotesting double negative results progressively increased with rescreening intervals of 1 to 9 years. Cervical cancer risks computed following any HPV-negative result, not considering cytology results, were consistently even higher at each comparable extended rescreening interval.

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Conclusions The PCCSM is a new data source that allows evaluation of cervical cancer risk over time. Cervical cancer risk is minimized with more frequent cytology and HPV cotesting.

Introduction

In March 2012, the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology released new guidelines for cervical screening, recommending "preferred" cytology and human papillomavirus (HPV) cotesting at 5-year intervals for women 30 years and older; Papanicolaou (Pap) testing at 3-year intervals was judged as "acceptable."[1] Cervical screening guidelines published later in 2012 by the American College of Obstetricians and Gynecologists were similar.[2] The US Preventive Services Task Force 2012 guidelines recommended either cotesting at 5-year intervals or cytology testing at 3-year intervals without preference.[3] In contrast, earlier 2006 and 2002 guidelines had recommended cotesting at 3-year intervals.[4,5] What led to the recommendations for a 5-year screening interval?

It has only recently been emphasized that the guideline development benchmark for "acceptable cervical cancer protection" in 2012 shifted from a higher level of protection provided with annual cytology testing to a measurably lower level of protection provided by cytology testing every 3 years.[6] Available studies comparing these options consistently document a relative increased cervical cancer risk with every 3-year versus annual screening in the range of 1.3 to 4.7 years.[6-12] Even as increased cervical cancer risks were discounted by guideline developers, there was increased emphasis on prevention of testing-associated "harms" and reliance on surrogate endpoints for cervical cancer risk, such as cervical intraepithelial neoplasia 3 (CIN3) or CIN3 or more severe lesions (CIN3+). Benchmarking of CIN3+ risk, based almost exclusively on data from Kaiser Permanente Northern California (KPNC), substantially drove the influential American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology guidelines process.[13] More recently, however, has it been acknowledged by several of the 2012 guidelines authors themselves that the surrogate endpoint of CIN3+ may be misleading as an outcome measure for population screening.[6] Accordingly, some of them have recently explicitly called for additional "data sources that permit examination of cervical cancer risks over time rather than surrogate endpoints."[6] In response to this call, we decided to use the large accumulated cervical screening database at Magee-Womens Hospital (MWH) of University of Pittsburgh Medical Center (UPMC), our proprietary Pittsburgh Cervical Cancer Screening Model (PCCSM),[14] a continuously updated dynamic Bayesian decision science tool, to further explore the impact of extended cervical screening intervals on invasive cervical cancer risk.

Materials and methods

This study was approved by the MWH Institutional Review Board (IRB# PRO09070454), Pittsburgh, Pennsylvania. The MWH-UPMC cytopathology laboratory reports over 100,000 cervical screening tests per year as part of a large subspecialized academic laboratory that serves an integrated health care system consisting of over 20 hospitals. The data we have analyzed were cervical screening data collected over 10 years (2005-2014) at MWH-UPMC. The data now include 976,624 liquid-based cytology (LBC) ThinPrep Pap test (Hologic Corp, Bedford, Massachusetts) results, 285,351 companion high-risk US Food and Drug Administration (FDA)-approved HPV test results (29.2%) (Hybrid Capture 2, Qiagen Corp, Gaithersburg, Maryland; Cervista, Hologic Corp, Madison, Wisconsin) from PreservCyt LBC vials, and 112,435 follow-up histopathologic results (11.5%) from surgical procedures that included cervical tissue sampling. These data derive from 325,795 women. In this study, we excluded vaginal cytology tests and patients who had only 1 recorded Pap test result with no recorded follow-up. ThinPrep Pap tests were routinely screened using the ThinPrep Imaging System.[15] This resulted in a final analysis of 727,716 cervical cytology test results from 200,306 women (average age 39.5 years).

Tables 1 and 2 show follow-up details for women with either LBC results or cotesting results for both LBC and HPV. Year 0 indicates the year when a woman for the first time has cervical screening. For all women in this database, diminishing subsets had recorded follow-up results in year

Table 1 Follow-up data: LBC test results for each year.

Year	Patients, n	Percentage
0	200,306	100.0
1	133,101	66.4
2	102,155	51.0
3	81,376	40.6
4	66,211	33.1
5	54,079	27.0
6	37,941	18.9
7	27,405	13.7
8	18,714	9.3
9	6,428	3.2

Abbreviation: LBC, liquid-based cytology.