The Pittsburgh Cervical Cancer Screening Model

A Risk Assessment Tool

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• ***Context.***—**Evaluation of cervical cancer screening has grown increasingly complex with the introduction of human papillomavirus (HPV) vaccination and newer screening technologies approved by the US Food and Drug Administration.**

Objective.—**To create a unique Pittsburgh Cervical Cancer Screening Model (PCCSM) that quantifies risk for histopathologic cervical precancer (cervical intraepithelial neoplasia [CIN] 2, CIN3, and adenocarcinoma in situ) and cervical cancer in an environment predominantly using newer screening technologies.**

Design.—**The PCCSM is a dynamic Bayesian network consisting of 19 variables available in the laboratory information system, including patient history data (most recent HPV vaccination data), Papanicolaou test results, high-risk HPV results, procedure data, and histopathologic results. The model's graphic structure was based on the published literature. Results from 375 441 patient records from 2005 through 2008 were used to build and train the model. Additional data from 45 930 patients were used to test the model.**

Conclusions.—**The PCCSM compares risk quantitatively over time for histopathologically verifiable CIN2, CIN3, adenocarcinoma in situ, and cervical cancer in screened patients for each current cytology result category and for each HPV result. For each current cytology result, HPV test results affect risk; however, the degree of cytologic abnormality remains the largest positive predictor of risk. Prior history also alters the CIN2, CIN3, adenocarcinoma in situ, and cervical cancer risk for patients with common current cytology and HPV test results. The PCCSM can also generate negative risk projections, estimating the likelihood of the absence of histopathologic CIN2, CIN3, adenocarcinoma in situ, and cervical cancer in screened patients.**

Conclusions.—**The PCCSM is a dynamic Bayesian network that computes quantitative cervical disease risk estimates for patients undergoing cervical screening. Continuously updatable with current system data, the PCCSM provides a new tool to monitor cervical disease risk in the evolving postvaccination era.**

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Evaluation of the factors involved in cervical cancer (CxCa) screening have grown increasingly complex with the introduction of human papillomavirus (HPV) vaccination[1] and the newer screening technologies approved by the US Food and Drug Administration (FDA). Use of HPV vaccines enter a CxCa screening environment that has shifted dramatically in the United States during the past 6 to 13 years with the introduction of FDA-approved liquid-based cytology (LBC),[2,3] computer-assisted screening,[4,5] widespread high-risk HPV (hrHPV) DNA reflex testing after findings of atypical squamous cells of undetermined significance (ASCUS) from Papanicolaou (Pap) tests,[6] and the introduction of Pap and HPV DNA cotesting in women 30 years and older.[7] The many testing and prevention options raise several new challenges when assessing how current test results and prior clinical history affect the risk stratification of individual patients.

We employed decision science tools of a dynamic Bayesian-network model analysis to form a unique Pittsburgh Cervical Cancer Screening Model (PCCSM)[8] that addresses these CxCa screening risk assessment challenges in an environment predominantly using the newer screening technologies now prevalent in the United States. The model is a dynamic Bayesian network that combines several sources of knowledge, including published medical literature, expert opinion, and extensive objective hospital data. The model is a convenient tool for assessing a patient's prospective risk for histopathologic diagnosis of cervical precancer (cervical intraepithelial neoplasia [CIN] 2, CIN3, and adenocarcinoma in situ [AIS]) or invasive CxCa. The model's quantitative assessments were initially constructed to assist in routine laboratory identification of patients at high risk for the quality-control rescreening mandated in federal regulations.[9] Furthermore, the model quantifies how multiple current testing and historic data variables together influence prospective risk for a histopathologic diagnosis of cervical precancer or invasive CxCa.

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The Magee-Womens Hospital Data From Test Results Collected During a 4-Year Period (2005–2008)					
	2005	2006	2007	2008	Total
Pap test results	97 144	111 019	113 197	100 011	421 371
hrHPV DNA test results	9120	18 652	30 150	23 926	81 848
Histopathologic data	11 009	10 590	11 798	11 718	45 115

Abbreviations: hrHPV, high-risk human papillomavirus; Pap, Papanicolaou.

MATERIALS AND METHODS

This study was approved by the Magee-Womens Hospital (MWH) Institutional Review Board (Pittsburgh, Pennsylvania). The data available for analysis consisted of 421 371 Pap test results collected during a 4-year period (2005–2008) at the MWH of the University of Pittsburgh Medical Center (Table). The MWH serves a significantly older-than-average,[10] relatively lower-risk, US population and uses LBC, location-guided computer-assisted screening, and HPV testing as its primary cervical screening tools. Most (97%–98%) of the Pap tests performed during the study period were liquid-based ThinPrep (Hologic Inc/Cytyc Corporation, Marlborough, Massachusetts) Pap tests, which were screened using the ThinPrep Imaging System (Hologic).[5] The reporting profile of the laboratory is documented in many recent publications.[11–16] Approximately 11% of cytology-screened cases were followed by surgical and histopathologic procedures (45 115 data entries), whereas about 19% of all cytologic data entries were associated with hrHPV DNA test results (81 848 hrHPV DNA test results). Some of the cases were accompanied by additional patient history data from screening test-requisition forms, which, most recently, included the history of HPV vaccination. The HPV vaccination history was first recorded by offices on Pap requisition forms in January 2008 and is the only new variable to be introduced during the 4-year study period. As of June 30, 2009, 841 patients have had a history of HPV vaccination recorded on Pap requisition forms. Depending on the historic variable, history data were available for 2% to 30% of all cytology entries. Each patient was further characterized by the demographic variables of age and race.

Dynamic Bayesian Networks

Bayesian networks,[17] also called *belief networks* or *causal networks*, are acyclic-directed graphs that model probabilistic influences among variables. The graphic part of a Bayesian network forms the structure of the modeled problem, whereas local interactions among neighboring probability distributions are quantified using actual system data. Bayesian networks have proven to be powerful tools for modeling complex problems involving uncertain knowledge. They have been practically employed in a wide variety of fields, including engineering, the physical sciences, and medicine, with some models reaching the size of hundreds or thousands of variables. Dynamic Bayesian networks are a temporal extension of Bayesian networks that allow for modeling of dynamic processes. The hidden Markov model is considered to be the simplest dynamic Bayesian network.[18] Considerable work on dynamic models in medicine has been carried out by Leong and collaborators,[19,20] who, in addition to developing Bayesian networks and dynamic Bayesian networks, have successfully used a combination of graphic models with Markov chains to address problems in different medical domains, including colorectal cancer management, neurosurgical intensive care unit monitoring, and cleft lip and palate management.[21] Other applications of dynamic Bayesian networks in medicine include NasoNet, a system for diagnosis and prognostication of nasopharyngeal cancer,[22] and a dynamic Bayesian network developed by investigators in the Netherlands for management of patients with carcinoid tumor.[23] Other reported biologic applications of dynamic Bayesian networks include predicting the secondary structure of a protein,[24] modeling peptide fragmentations[25] and cellular systems,[26] and identifying gene regulatory networks from time-course, microarray data.[27]

Pittsburgh Cervical Cancer Screening Model

The PCCSM is a dynamic Bayesian network consisting of 19 variables, including the Bethesda System[28] cytologic variables (source of Pap test, Pap test type, Pap test result, and Pap test adequacy category), histopathologic and surgical data (surgical procedures and histopathologic results), and hrHPV DNA test results (as positive, negative, or not available). The model also includes patient history data available in the laboratory information system, such as history of infections, history of cancer, history of contraception, history of abnormal cytology, menstrual history, HPV vaccination history since January 2008, and the demographics age and race. We based the structure of the model, that is, the interactions among the modeled variables, on existing published medical evidence enhanced with expert opinion and independence tests performed on patient records. Most of the variables were discrete. The only continuous variable (age) was discretized into 5 intervals: younger than 20, 20 to 29, 30 to 44, 45 to 59, and 60 years and older. Figure 1 represents the graphic structure of a static version of the PCCSM, which preceded the building of a dynamic version of the model capable of computing future risk estimates. The model was quantitatively parameterized by means of training data collected for almost 4 full years (2005–2008) and consisting of 375 441 patient records. The model was created and tested using SMILE (Structural Modeling, Inference, and Learning Engine), an inference engine, and GeNIe, a development environment for reasoning in graphic probabilistic models, both developed in the Decision Systems Laboratory of the University of Pittsburgh and available in the public domain at no cost to users (http://genie.sis.pitt.edu/; accessed October 20, 2009). After building and training the model, 45 930 patient cases from a 5-month period (April–August 2008) not included in the training data set were analyzed. Patient ages ranged from 12 to 95 years (mean, 42.17 years; SD, 15.71). Current cytology result data from these patients were entered into the model along with patient history findings and current available hrHPV DNA test results. These data are referred to as *testing data*. The dynamic PCCSM can generate CIN2, CIN3, AIS, and CxCa risk projections over variable future periods. Results presented in the following section represent the projected risk for histopathologically verifiable CIN2, CIN3, AIS, and CxCa over specified periods, ranging from the time of screening to 3 years. Quantitative outputs of the PCCSM can be further analyzed with statistical tests of significance (eg, *Z* tests, analyses of variance).[29] Risk projections for different categories of current cytologic and HPV results can be compared to investigate whether or not risk variations between specific groups of patients are statistically significant.

RESULTS

Given current available cytology and HPV test results and patient history data, the PCCSM was first used to estimate the relative risk of histopathologically verifiable CIN2, CIN3, AIS, and CxCa for groups of individuals, with each discrete Bethesda System category of current cytologic result and each possible current hrHPV DNA test result category (positive, negative, or not available). Figure 2 shows quantitative relative risk projections at 2 years. Quantitative risk projections varied substantially according to the degree of current cytologic abnormality. Risk also varied according to hrHPV DNA test status. The degree of cytologic abnormality was the largest positive predictor of histopathologic precancer or CxCa risk, whether or not hrHPV DNA test results were available. The highest risk was projected for the group of patients with current cytologic findings of high-grade squamous intraepithelial

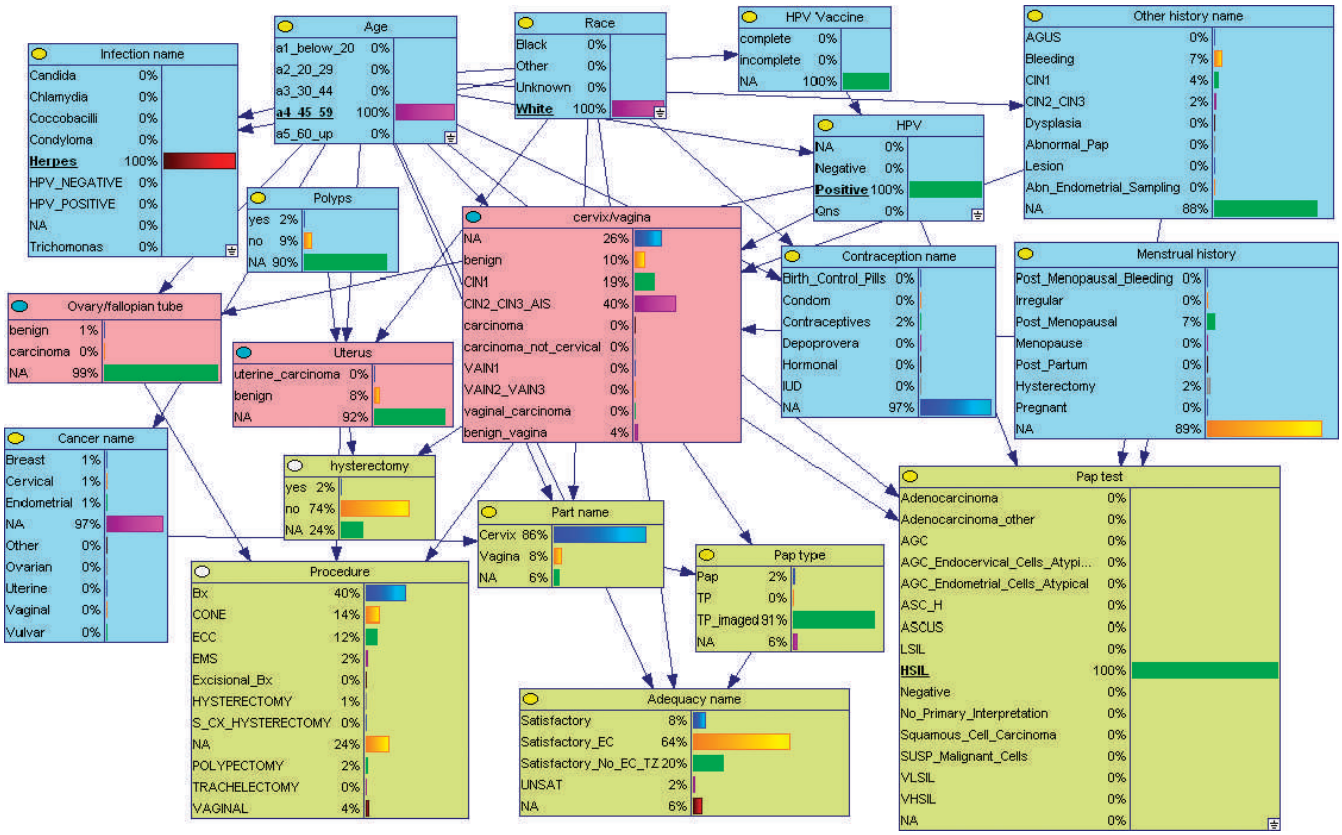


Figure 1. *Graphic structure of static version of the Pittsburgh Cervical Cancer Screening Model. Abbreviations: AGC, atypical glandular cells; AGUS, atypical glandular cells of undetermined significance; ASCUS, atypical squamous cells of undetermined significance; ASC_H, atypical squamous cells, cannot exclude HSIL; Bx, cervical biopsy; CIN1, cervical intraepithelial neoplasia 1; CIN2_CIN3_AIS, histopathologic cervical precancer; CONE, cervical cone biopsy; ECC, endocervical curettage; EMS, endometrial sampling; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; IUD, intrauterine device; LSIL, low-grade squamous intraepithelial lesion; NA, not available; Pap, Papanicolaou test; QNS, quantity not sufficient; S_CX_HYSTERECTOMY, supracervical hysterectomy; SUSP_Malignant_Cells, suspicious for malignant cells; TP, ThinPrep Papanicolaou test; TP_imaged, ThinPrep Papanicolaou test using the ThinPrep Imaging System; Satisfactory_EC, Papanicolaou test adequacy satisfactory, endocervical/transformation zone component present; Statisfactory_NO_EC_TZ, Papanicolaou adequacy satisfactory, endocervical/transformation zone component absent; UNSAT, Papanicolaou test adequacy unsatisfactory; VAIN1, vaginal intraepithelial neoplasia 1; VAIN2_VAIN3, vaginal intraepithelial neoplasia 2, vaginal intraepithelial neoplasia 3; VHSIL, vaginal high-grade squamous intraepithelial lesion; VLSIL, vaginal low-grade squamous intraepithelial lesion.*

lesions or worse (including cytologic findings of cancer or cytologic findings suspicious for cancer) and those with a positive hrHPV DNA test result. The lowest risk was projected for the group of patients with current negative cytology results and those who had negative findings for hrHPV DNA cotest results. Other combinations of cytology results and hrHPV DNA test results, including no HPV test result available, showed intermediate risk projections, as presented in Figure 2, arranged with lower risk levels on the right and higher risk levels on the left.

Effect of Prior History on CIN2, CIN3, AIS, and CxCa Risk

The PCCSM was next used to assess the effect of different prior history records on quantitative risk for histopathologic CIN2, CIN3, AIS, and CxCa of patients with common current Pap and HPV results. The PCCSM allows the entry for each patient to include all available history from the 2004 to 2008 study period. Figure 3 shows the 2-year relative-risk projections for histopathologic CIN2, CIN3, AIS, and CxCa for patients presenting with current ASCUS Pap and positive hrHPV DNA test results. Model results showed that risk varied substantially with different patient history. For example, patients with all previously negative findings on Pap tests constituted the lowest-risk group, whereas those patients who, in the past, had any histopathologically verified CIN2, CIN3, AIS, or CxCa or any cytologic high-grade squamous intraepithelial lesion results constituted the highest-risk group. Figure 4 similarly shows that the 2-year relative risk for CIN2, CIN3, AIS, and CxCa also varied with different prior history records for patients with current ASCUS Pap test and negative hrHPV DNA test results; however, the levels of risk were generally lower than those shown in Figure 3 for patients with current ASCUS Pap test results and a positive hrHPV DNA test result.

The PCCSM was also used to estimate the negative predictive value of current test results. Figure 5 shows model projections for the likelihood of *not* having a histopathologic diagnosis of CIN2, CIN3, AIS, and CxCa over periods ranging from 1 to 3 years for 5 groups with various combinations of current low-risk screening test results. Figure 5 includes projections for patients with current negative Pap and current negative hrHPV DNA cotest results, for those with current negative Pap results and no available current hrHPV DNA test results, for those with any current Pap result and current negative hrHPV DNA test results, for those with current ASCUS Pap results and negative reflex hrHPV DNA test results, and finally for

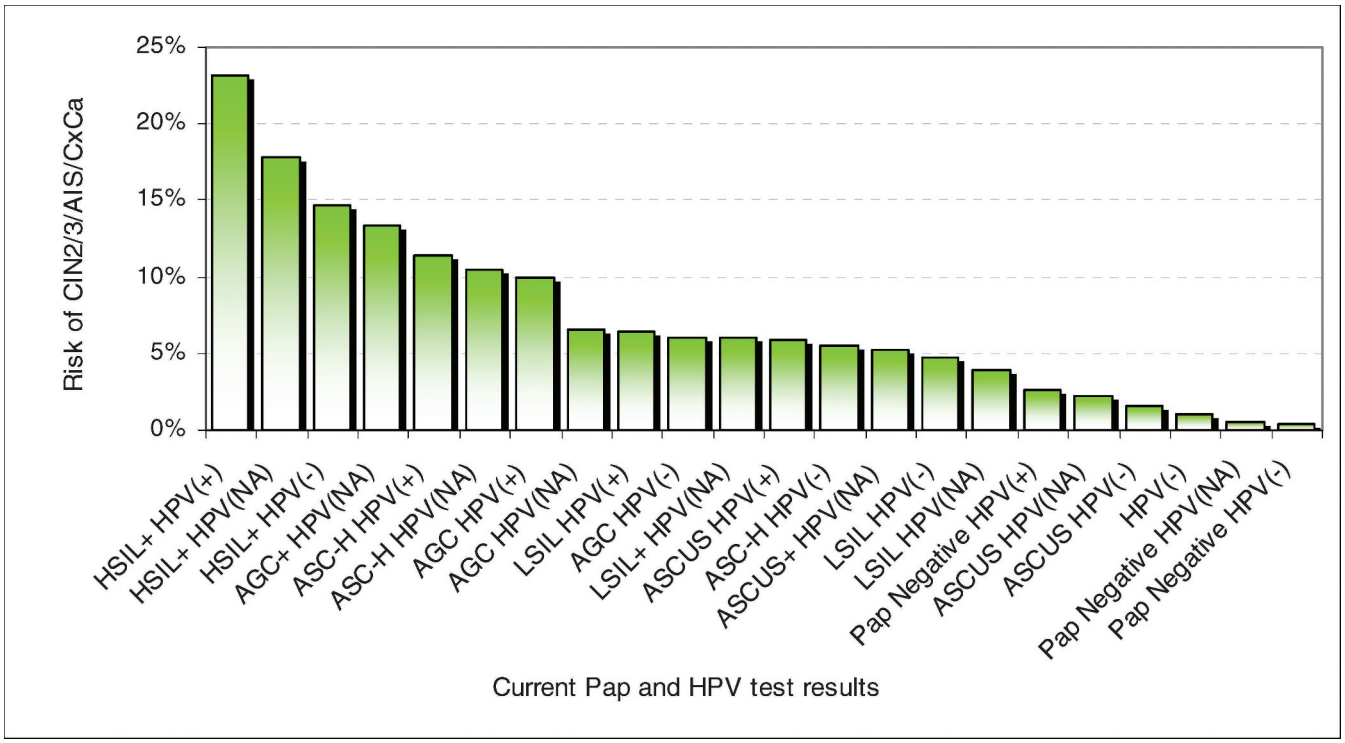


Figure 2. *Relative-risk projections for histopathologic precancer and invasive cervical cancer at 2 years (ordered from highest to lowest risk) with different current Papanicolaou and human papillomavirus test results. Abbreviations: AGC+, atypical glandular cells or worse (AGC, ASC-H, HSIL, suspicious, or cancer); ASC-H+, atypical squamous cells, cannot exclude HSIL or worse (ASC-H, HSIL, suspicious, or cancer); ASCUS+, atypical squamous cells of undetermined significance or worse (ASCUS and all other abnormal cytology results); CIN2/CIN3/AIS/CxCa, cervical precancer and invasive cervical cancer; HPV, human papillomavirus; HPV(+), positive HPV test result; HPV(−), negative HPV test result; HPV(NA), HPV test result not available; HSIL+, high-grade squamous intraepithelial lesion or worse (HSIL, suspicious, or cancer); LSIL+, low-grade squamous intraepithelial lesion or worse (LSIL, AGC, ASC-H, HSIL, suspicious, or cancer); Pap, Papanicolaou test.*

those with current negative Pap and positive hrHPV DNA combined test results. The greatest likelihood for absence of a CIN2, CIN3, AIS, and CxCa diagnosis was in the group with current negative Pap and HPV cotest results. Even though results appear similar in Figure 5 for the group with negative Pap results and no HPV test results available (NA), statistical analysis confirmed that each of the slightly higher negative predictive values associated with double-negative Pap and HPV cotest results was statistically significant (Z test, $P < .01$).

COMMENT

The PCCSM constitutes a large, dynamic Bayesian network–modeled database that reflects prevalent, current use in the United States of newer, FDA-approved screening technologies.[2,5–7] The model allows for computation of quantitative estimates of the effect of multiple variables of risk for a studied diagnostic outcome, that is, detection of histopathologic cervical precancer (CIN2, CIN3, or AIS) and invasive CxCa. The model, therefore, is able to identify groups of patients who are at progressively lower or higher risk for having a subsequent histopathologic diagnosis of CIN2, CIN3, AIS, and CxCa. Furthermore, the PCCSM prospective-risk projections reflect not only variable combinations of current screening test results but also prior history data.

A number of modeling approaches to CxCa have been reported to address questions about the role and cost-effectiveness of new screening or prevention techniques, optimal screening frequency, the potential of risk-adapted screening policies, and adherence to screening policy.[30–36] These models have primarily been transition models that simulate the natural history of disease. Such models have been widely used and regarded as valid approaches for epidemiologic projections and as guidance for CxCa screening, diagnosis, and treatment decisions. One significant limitation of many modeling approaches has been reliance on published, older, historic, and international data sets, which may precede or differ substantially from newer, FDA-approved, cervical screening methods of the modern era that are in widespread use and are prevalent in the United States, including liquid-based cytology, computer-assisted imaging, and adjunctive HPV reflex or routine cotesting.[2–7] According to manufacturer estimates reported periodically to the Securities and Exchange Commission, LBC now comprises around 95% of the annual US Pap-test market, and computer-assisted imaging is being used on most of those samples. More than 85% of findings of ASCUS from Pap tests in the United States are now being followed by reflex HPV testing, and more than 25% to 30% of women 30 years and older are being routinely screened with cytology and HPV cotesting. Older data sets may also not reflect the significantly increasing glandular histology of CxCa noted in the United States and elsewhere during the past several decades.[37,38] The PCCSM is the first reported model, to our knowledge, based on extensive, recent, US data using newer, FDA-approved, cervical screening technologies.[11–15] Reliance of models on international data from health systems where screening methods and policies on

Figure 3. *Two-year relative-risk projections for histopathologic precancer and invasive cervical cancer for current ASCUS high-risk human papillomavirus DNA⁺ screening test results with different history records. Abbreviations: AGC, atypical glandular cells; ASC-H, atypical squamous cells, cannot exclude HSIL; ASCUS, atypical squamous cells of undetermined significance; CIN2/3/AIS/CxCa, cervical precancer and invasive cervical cancer; HPV, human papillomavirus; HPV(+), positive HPV test result; HPV(−), negative HPV test result; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; Pap, Papanicolaou test.*

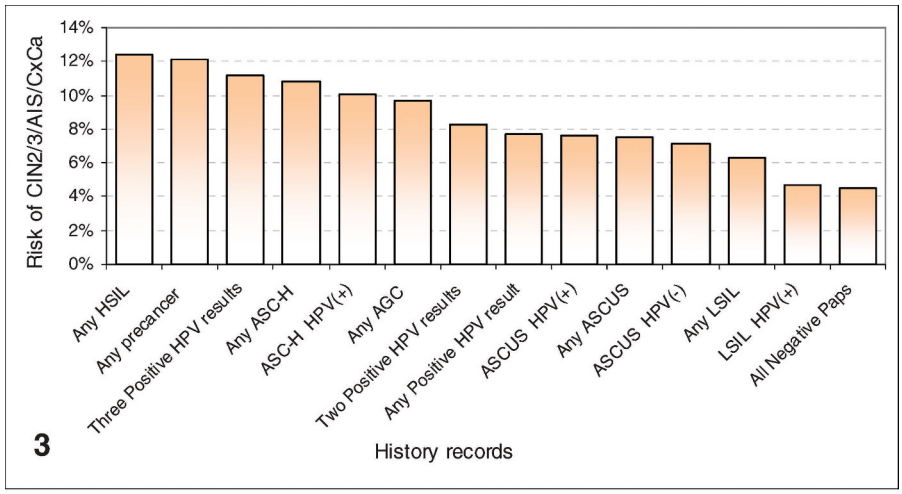
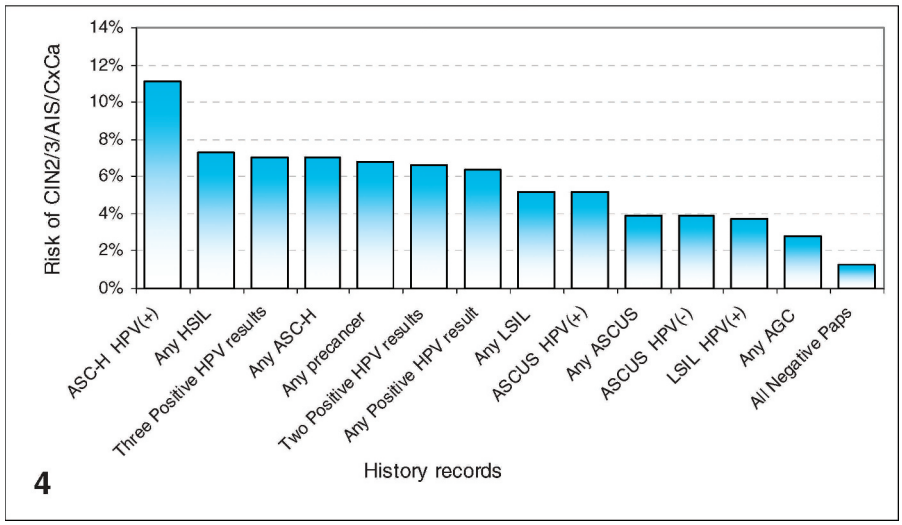


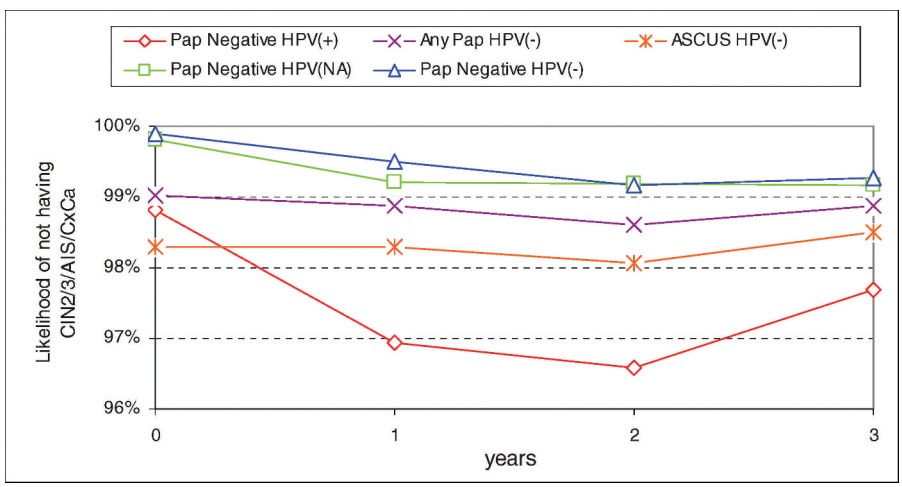
Figure 4. *Two-year relative risk projections for histopathologic precancer and invasive cervical cancer for current atypical squamous cells of undetermined significance high-risk human papillomavirus DNA⁻ screening test results with different history records. Abbreviations: AGC, atypical glandular cells; ASC-H, atypical squamous cells, cannot exclude HSIL; ASCUS, atypical squamous cells of undetermined significance; CIN2/3/AIS/CxCa, cervical precancer and invasive cervical cancer; HPV, human papillomavirus; HPV(+), positive HPV test result; HPV(−), negative HPV test result; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; Pap, Papanicolaou test.*



screening frequency, follow-up, and treatment are substantially different from the United States may have less application in the United States.[39,40]

Both the current and intermediate (1–3 years) future risk of histopathologic CIN2, CIN3, AIS, or CxCa diagnoses in the PCCSM were most strongly correlated with the degree of cytologic abnormality. These observations are consistent with numerous published observations on the positive predictive value of cervical cytology.[39] The PCCSM projections also reflect the utility of adjunctive HPV cotesting with equivocal abnormal cytology results because the combination of equivocally abnormal cytology and positive HPV test results show increased positive predictive values, which support diagnostic testing referral, whereas the negative predictive value of negative HPV tests allows efficient triage of patients to routine,

Figure 5. *Likelihood of not having histopathologic precancer or invasive cervical cancer within 3 years. Abbreviations: ASCUS, atypical squamous cells of undetermined significance; CIN2/3/AIS/CxCa, cervical precancer and invasive cervical cancer; HPV, human papillomavirus; HPV(+), positive HPV test result; HPV(−), negative HPV test result; HPV(NA), HPV test result not available; LSIL, low-grade squamous intraepithelial lesion; Pap, Papanicolaou test.*



periodic retest screening.[6,13] The quantitative effects of prior history on risk projections for patients with common current cytology and HPV test results (Figures 3 and 4) has not, to our knowledge, been previously reported but is generally consistent with the broad literature indicating the effect of prior history on future risk.[41,42] The PCCSM projections of high, negative predictive value for double-negative (cytology negative and hrHPV negative cotest results) are also consistent with observations that patients with both negative Pap test and hrHPV test results are at very low risk for current or prospective diagnosis of cervical precancer or CxCa.[43,44] The high, negative predictive values projected by the PCCSM for imaged LBC are consistent with recently published results reflecting the use of imaging and LBC[11,12] and with recent international clinical trial data using LBC.[45] The PCCSM projections differ from some other results reported in screening trials using manually screened conventional Pap smears.[46] These observations emphasize the importance of examining data sets reflecting the use of newer, FDA-approved screening technologies.

Beginning in January 2008, the University of Pittsburgh Medical Center Pap test requisition forms began listing HPV vaccination history among clinical history variables to be potentially checked off by system cervical screening providers and office staff. Since then, 841 patients have had this history recorded on Pap test requisition slips. This small number of data entries has not yet measurably affected PCCSM risk projections. Although this method of documenting HPV vaccination history clearly has major limitations, nevertheless the continuously updated risk projections of the PCCSM should prove to be of great interest over time as a new modeling method to assess postvaccination screening strategies.[31,47] Furthermore, the vaccination component of the database could be updated in the future if a local or national vaccine registry were to be developed. The PCCSM quantitative risk assessments may also prove to be of use in the future as a personalized aid in clinical management and follow-up decision-making. Early efforts exploring these possibilities are underway in our health system. The PCCSM identifies numerous promising paths for research and investigation.

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