Risk Stratification Using Human Papillomavirus Testing among Women with Equivocally Abnormal Cytology: Results from a State-Wide Surveillance Program

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Abstract

Background: Clinical guidelines for cervical cancer screening have incorporated comparative risks of cervical intraepithelial neoplasia grade 3 or cancer (CIN3+) for various screening outcomes to determine management. Few cohorts are large enough to distinguish CIN3+ risks among women with minor abnormalities versus negative cytology because of low incidence. The New Mexico Human Papillomavirus (HPV) Pap Registry offers a unique opportunity to evaluate cervical cancer screening in a diverse population across a broad-spectrum of health service delivery.

Methods: Kaplan–Meier and logistic–Weibull survival models were used to estimate cumulative risks of CIN3+ among women ages 21 to 64 who were screened in New Mexico between 2007 and 2011 with negative, equivocal or mildly abnormal cytology, that is, atypical squamous cells of undetermined significance (ASC-US); with or without HPV triage), or low-grade squamous intraepithelial lesions (LSIL).

Results: We identified 452,045 women meeting the selection criteria. The 3-year CIN3+ risks for women with negative, ASC-US, and LSIL cytology were 0.30%, 2.6%, and 5.2%, respectively. HPV triage of ASC-US stratified 3-year CIN3+ risks were 0.72% for HPV-negative and 7.7% for HPV-positive. Risks tended to decline after age 30 for all screening results.

Conclusions: In this state-wide population-based cohort, cytology and HPV triage of ASC-US stratified women’s CIN3+ risk into similar patterns observed previously, suggesting the validity of screening guidelines for diverse populations in the United States. Absolute risk estimates should be compared across other large populations.


Introduction

In the United States, cervical cancer incidence has been dramatically reduced through widespread implementation of frequent cervical cytology using Papanicolaou (Pap) testing. With the increased understanding of the natural history of cervical carcinogenesis, biomarkers are emerging that might better stratify the risk of cervical precancer (cervical intraepithelial neoplasia grade 3) and cancer (CIN3+) and reduce frequency of screening. As professional societies consider how to incorporate new biomarkers such as human papillomavirus (HPV) testing into cervical cancer screening and management, they are using comparative risks of CIN3+ to help determine management recommendations in practice guidelines. In 2013, the American Society for Colposcopy and Cervical Pathology (ASCCP) created management guidelines for women with abnormal cervical screening results (1). Using the principal of “equal management of women with equal risks” (2), the risks of CIN3+ and cancer were compared between women with different screening results to determine appropriate management. Although the management of high-grade cytologic abnormalities (immediate colposcopic referral) is rather non-controversial, determining appropriate management of negative or mildly abnormal (i.e., ASC-US HPV+, or LSIL) screening results has been more complicated. Unfortunately, because very large populations with long-term follow-up are needed, it can be difficult to obtain precise risk estimates for negative and mildly abnormal cervical screening results that carry a low risk of CIN3+. Large longitudinal cohorts are ideal because they are sufficiently powered to detect CIN3+ at sequential screening rounds. For the ASCCP management guidelines...
review, data were primarily considered from one source, that is, from women undergoing cervical screening at Kaiser Permanente Northern California (KPNC), a large integrated health delivery system that has practiced standardized routine cotesting (cervical cytology and HPV testing together) since 2003 (3).

However, the application of risk assessment for benchmarking for cervical cancer screening has not been entirely straightforward because absolute risk estimates after negative and mildly abnormal screening results have differed between KPNC and two large U.S. randomized controlled trials, the Atypical Squamous Cells of Undetermined Significance (ASCUS)/LSIL Triage Study (ALTS) and the Addressing the Need for Advanced HPV Diagnostics (ATHENA) study (3–5). The reasons for these differences are not certain, but might relate to the differences between population-based screening cohorts and clinical trials. Therefore, risk estimates in other large population-based cohorts are critically needed.

The New Mexico Human Papillomavirus (HPV) Pap Registry (NMHPVPR) offers a unique opportunity to calculate cumulative CIN3+ risk in a state-wide population and compare with KPNC. The registry represents a heterogeneous population from across New Mexico providing cervical cancer screening within diverse health care settings. The registry was established in 2006, providing sufficient follow-up time to generate cumulative risk estimates for women with negative or mildly abnormal cervical screening results.

As a separate, important methodologic issue, the optimal way to estimate current and future risks of CIN3+ from medical records data has not been identified. The traditional Kaplan–Meier (KM) approach measures when disease is first detected while the logistic–Weibull model attempts to estimate when disease first occurs and incorporates interval-censoring of disease outcomes between screening tests. To better understand how these models compare with one another, we sought to utilize and compare both strategies (2, 6).

### Materials and Methods

#### Registry

The NMHPVPR is a public health surveillance activity established to evaluate the continuum of cervical cancer prevention throughout the state. The structure of the NMHPVPR has been described previously (7). Under state regulation, laboratories must report to the NMHPVPR all results of cervical cytology, cervical pathology, and HPV tests as well as vulvar and vaginal pathology performed on New Mexico residents (8). Ongoing evaluations of cervical screening, diagnosis, and treatment by the NMHPVPR have been reviewed and approved under exempt status by the University of New Mexico Human Research Review Committee. The National Institutes of Health Office of Human Subjects Research deemed this study exempt from Institutional Review Board review.

Cervical cytology and HPV results were ascertainment for the period January 1, 2007, to December 31, 2011, from nine laboratories in New Mexico and nine out-of-state laboratories that serve New Mexico residents. All hospitals and clinical practices in New Mexico report through these laboratories. Probabilistic matching and linking of different tests to the same woman was performed and augmented by manual reviews when linkage was uncertain (8).

#### Study population and outcomes

Our analysis included women ages 21 to 64 with a negative, ASC-US or LSIL baseline cervical screening result reported during January 1, 2007, to December 31, 2011. Women were excluded if records indicated that they had a prior cervical cytology within 300 days of their baseline screening cytology (suggesting that the baseline test was a follow-up rather than screening test) or if they had a cervical excisional procedure (i.e., loop electro surgical excisional procedure [LEEP] or cone biopsy) or hysterectomy, prior to their baseline screening cytology (7, 9). Women with an abnormal baseline cytology and no subsequent follow-up were excluded from all analyses. Women were followed through electronic and paper medical records submitted to the NMHPVPR (10). The outcomes were defined by local community readings of histopathology results from biopsy, endocervical curettage, excisional procedure, or hysterectomy without central review from the date of baseline screening through December 31, 2013. An outcome of cervical intraepithelial neoplasia (CIN) grade 2 or worse (CIN2+) included results of CIN1-2, CIN2, CIN2-3, CIN3, CIS, adenocarcinoma in situ (AIS), squamous-cell carcinoma, or high grade (not otherwise specified [NOS]). An outcome of CIN3+ was defined as a result of CIN2-3, CIN3, CIS, AIS, or squamous-cell carcinoma. Adenocarcinomas (n = 114) were excluded from this report due to ongoing work related to potential misclassifications of cervical and endometrial adenocarcinomas. Follow-up outcomes were terminated at the date of an excisional procedure, or hysterectomy.

#### Statistical methods

We estimated the cumulative incidence of histological outcomes of CIN2+ and CIN3+ for each cervical cytology result (normal, ASC-US or LSIL). We concentrate on risk of CIN3+ whereas CIN2+, a less reproducible diagnosis of precursor, is included for completeness. We also calculated risks for women with ASC-US and a concurrent HPV test result (ASC-US/HPV-positive or ASC-US/HPV-negative). We compared two different analytic approaches to validate the conclusions.

First, we used the standard KM approach commonly used in these analyses (11–13). Time to event was defined as the number of months between the baseline cytology test and the date of histologic diagnosis of CIN2+ or CIN3+. Women without CIN2+ or CIN3+ were right censored at the later of the last known cytology test or cervical biopsy. Because the KM approach measures time to detection of CIN when a woman returns for biopsy, it inherently does not estimate prevalent disease rise and it underestimates risk at very early time intervals. The KM method also regards the unobserved interval-censored time of onset of disease to be the time of diagnosis, resulting in bias for interval-censored outcomes (14, 15). Consequently, we compared the KM method with a logistic–Weibull model.

The logistic–Weibull model was used to analyze data from Kaiser Permanente Northern California (KPNC) and the technical aspects of the analysis are described in the supplementary Web Appendix of those papers (2, 6) and Supplementary Materials to this paper. The cumulative risk was calculated as the sum of risk at the baseline cervical cytology (plotted at time zero on each figure) and the incidence after baseline. For nonnegative baseline cervical cytology results, the risk at baseline was computed as the proportion of all women with a histologic diagnosis of CIN2+ or CIN3+ on or after the baseline cytology test and before any subsequent screening cytology test, negative follow-up cytology, CIN3...
or negative biopsy (in general, baseline risk is estimated from a logistic regression model). Among women without baseline CIN2, we used Weibull survival models (14) with interval censoring to estimate risk over time. Weibull models can make smoother and more accurate risk estimates than nonparametric methods for interval censoring (15). We assigned each CIN2+ to have occurred between the second-to-last screening visit and the biopsy visit where the CIN2+ was diagnosed. For negative baseline cervical cytology results (irrespective of HPV result), biopsies are not performed and thus the baseline risk is forced to be zero, and then the interval-censored Weibull model is applied as above to calculate risk over time. For negative cytology, we focus solely on the critical estimates of cumulative 3- and 5-year risks.

Separate models, from both approaches, were fit for each cervical screening result (negative, ASC-US, LSIL, HPV-positive/ASC-US, and HPV-negative/ASC-US) among women in 5-year age groups (21–24, 25–29 years, etc.). This age range was selected for comparison with similar population-based analyses of risk in the United States (2). Five-year cumulative risk estimates were compared between cervical screening results using a two-sample z-statistic on the complementary log–log scale transformed cumulative risk. We used weighted least squares regression on the complementary log–log scale transformed logistic–Weibull estimates of 5-year cumulative risk to compute a test for trend across age groups [21–29, 30–39, 40–49, and 50–64]. SAS version 9.3 was used for all analyses. P value of <0.05 was considered statistically significant.

Results

Between January 2007 and December 31, 2011, we identified 452,045 women ages 21 to 64 years with a baseline screening cytology of LSIL (n = 8,211), ASC-US (n = 20,117), or negative (n = 423,717; Table 1). A concurrent or reflex HPV test was available for 15,724 (78.2%) of women with an ASC-US result, of whom 41.0% (n = 6,451) tested HPV-positive. (N.B., we know from separate data on a group basis that over 95% of HPV tests were Hybrid Capture, Qiagen, Germantown, MD.) An additional 4,474 women had a cytology result worse than LSIL (i.e., atypical glandular cells [AGC], atypical squamous cells cannot rule out high-grade [ASC-H], high-grade squamous intraepithelial lesion [HSIL], squamous cell carcinoma [SCC]) and were excluded from this analysis. Approximately one-quarter of the women (n = 126,560) did not have any follow-up (cytology test, cervical biopsy, excisional procedure, or hysterectomy) beyond the baseline screening cytology. Women with an HPV-positive/ASC-US or LSIL cytology were more likely to have follow-up data. Stratified analyses showed that among women with a negative screening result, those age 50 to 64 were also less likely to have follow-up data. This might be due to less frequent screening at older ages or incomplete ascertainment of hysterectomy. Patterns of follow-up by age and cytology were not confounded by year of baseline cytology.

For the other 325,485 women, the mean follow-up time was 3.69 years (SD = 1.69, median = 3.83, IQR = 2.32–5.10). The total follow-up time was 1,201,734 person-years. Women with an LSIL or HPV-positive/ASC-US result were more likely to be in the youngest age categories (age 21–29) compared to women with an HPV-negative/ASC-US or cytology-negative result (59.3% vs. 25.9%, P < 0.001).

The cumulative risks of CIN2+ and CIN3+ among women ages 21 to 64 years are plotted in Fig. 1A and B and detailed further in Supplementary Tables S1 and S2 for the KM and logistic–Weibull estimates. Anticipated patterns were observed between KM and logistic–Weibull estimates of baseline risk and risk estimates were similar by year 3. The CIN2+ and CIN3+ risks after an HPV-positive/ASC-US result were similar to risks after an LSIL result (logistic–Weibull model; 3-year risk: 15.7% vs. 15.2%, P = 0.5 for CIN2+ and 6.0% vs. 5.2%, P = 0.04 for CIN3+; 5-year risk: 18.7% vs. 17.9%, P = 0.3 for CIN2+ and 7.7% vs. 6.5%, P = 0.03 for CIN3+). CIN3+ risks among women with an HPV-negative/ASC-US were only slightly higher than for women with a negative cytology result (logistic–Weibull model; 3-year risk: 0.38% vs. 0.30%, P = 0.2; 5-year risk: 0.72% vs. 0.52%, P = 0.05).

Figure 2 shows the age-stratified cumulative risks of CIN2+ and CIN3+ at 5 years after baseline cervical screening. Across all baseline screening results, a similar pattern of risk stratification was observed across ages for younger and older women. That is, the HPV-positive/ASC-US results were associated with risks higher than or close to LSIL results and HPV-negative/ASC-US results were similar to negative cytology. One exception was among women ages 50 to 64 years where women with an LSIL result had a substantially lower CIN3+ risk than women with an HPV-positive/ASC-US result (logistic–Weibull model: 1.4% vs. 4.7%, P = 0.009).

In general, 5-year CIN3+ risks were highest at age 30 to 39 years for women with HPV-positive/ASC-US or LSIL (“positive screening results”) and then dropped in older age groups. For women with HPV-negative/ASC-US or Pap-negative results (“negative screening results”) and then dropped in older age groups.

### Table 1. Distribution of baseline mildly abnormal or normal cervical screening result (2007–2011) by age

<table>
<thead>
<tr>
<th>Age at baseline (years)</th>
<th>Total N</th>
<th>LSIL N (row %)</th>
<th>HPV-positive/ASC-US N (row %)</th>
<th>HPV-negative/ASC-US N (row %)</th>
<th>HPV-unknown/ASC-US N (row %)</th>
<th>Cytology-negative N (row %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>456,519</td>
<td>8,211</td>
<td>6,451</td>
<td>9,273</td>
<td>4,393</td>
<td>423,717</td>
</tr>
<tr>
<td>21–24</td>
<td>58,182</td>
<td>2,929 (5.0%)</td>
<td>2,120 (3.6%)</td>
<td>1,044 (1.8%)</td>
<td>957 (1.6%)</td>
<td>50,408 (86.6%)</td>
</tr>
<tr>
<td>25–29</td>
<td>66,142</td>
<td>2,021 (3.1%)</td>
<td>1,631 (2.5%)</td>
<td>1,285 (2.0%)</td>
<td>755 (1.2%)</td>
<td>59,604 (90.1%)</td>
</tr>
<tr>
<td>30–39</td>
<td>106,892</td>
<td>1,758 (1.6%)</td>
<td>1,410 (1.3%)</td>
<td>2,356 (2.2%)</td>
<td>967 (0.9%)</td>
<td>99,245 (92.8%)</td>
</tr>
<tr>
<td>40–49</td>
<td>103,671</td>
<td>855 (0.8%)</td>
<td>747 (0.7%)</td>
<td>2,566 (2.5%)</td>
<td>917 (0.9%)</td>
<td>97,638 (94.2%)</td>
</tr>
<tr>
<td>50–64</td>
<td>21,832</td>
<td>648 (0.5%)</td>
<td>543 (0.4%)</td>
<td>2,022 (1.7%)</td>
<td>797 (0.7%)</td>
<td>116,822 (96.0%)</td>
</tr>
</tbody>
</table>

NOTE: Women with abnormal cytology results worse than LSIL (AGC, ASC-H, HSIL, or SCC) are not presented in this table: 724 women age 21-24, 846 women age 25-29, 1,156 women age 30-39, 948 women age 40-49, and 800 women age 50-54. Abbreviations: LSIL, low-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; AGC, atypical glandular cells; ASC-H, atypical squamous cells cannot rule out high-grade; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma.
screening results), the 5-year CIN3⁺ risks declined steadily with age. CIN2⁺ risks followed a similar age trend across screening results with the exception of women testing HPV-negative/ASC-US, where the decline of risk with older age was statistically significant (logistic–Weibull model, $P = 0.03$).

**Discussion**

The results from our analysis of 5-year risk of CIN2⁺ and CIN3⁺ among 450,000+ women with cervical cytology screening in New Mexico between 2007 and 2011 corroborates and
extends to a state-wide population-based evaluation, the strong risk stratification provided by HPV triage of ASC-US cytology (3–5, 16). The CIN3+ risk among women with HPV-positive/ASC-US screening cytology is similar to risks among women with an LSIL screening cytology whereas the risk among women with HPV-negative/ASC-US screening cytology approximates the risk among women with a negative screening cytology. This trend was consistently observed across all ages with the exception of women age 50 to 64 with an LSIL screening cytology for whom the risk was closer to risks after a negative screening cytology. Because the CIN3+ risks for the screening cytology results at NMHPVPR had a similar hierarchical ranking to the CIN3+ risks observed for the same screening cytology results in other cohorts (3–5), the risk benchmarking methodology when applied across cohorts will apparently result in the same patient management recommendations.

As seen in other cohorts, the cumulative CIN2+ and CIN3+ risks following negative or mildly abnormal cytology results either declined or remained constant with increasing age (3). The observed decline in risk among older women, particularly those approaching the age of menopause and later, should be considered cautiously as CIN2 and CIN3+ can be more challenging to detect among older women (17, 18). In addition, the analysis corrected for benign hysterectomy, ascertainment of hysterectomy data was likely incomplete. The CIN3+ risk associated with LSIL cytology was notably lower among women ages 50 to 64 years. This may be partially explained by the observed lower HPV positivity rate among women age 45 and older (19), but HPV testing results are not routinely available as they would be if women were undergoing cotesting, which was uncommon in New Mexico during the period of study (7).

NMHPVPR represents a typical opportunistic screening scenario common to the United States, with great diversity in health plans, clinical practice settings, providers, and patients. By nature, the NMHPVPR state-wide setting includes great variability in patient management, pathology, and HPV laboratories (20). Higher CIN3+ risks have been observed in screening trials of HPV-based screening (4, 21, 22). This might be caused by better immediate disease ascertainment including the greater intensity of follow-up and more frequent sampling and random biopsy in screening trials compared with routine clinical management in NMHPVPR, different population characteristics or random variation.

Our analysis explored two different approaches to risk estimation of CIN2+ and CIN3+ after screening. As expected, the KM estimates of immediate risk were lower because they are measuring time to detection of CIN rather than time of occurrence. It is uncertain to what extent the logistic–Weibull estimates were precise in estimations of baseline risk. Fortunately, both methods had similar estimates by year 3 in our analyses. One limitation of both the KM and logistic–Weibull risk estimations is that they do not account for any change in the natural history of disease associated with any intervention; for example, disease modification by procedures associated with biopsy and treatment of CIN1 or CIN2 (23).

In conclusion, our analysis of 5-year cumulative CIN2+ and CIN3+ risks by baseline screening results from the NMHPVPR confirms and extends the hierarchy of risks observed in other United States screening cohorts (3–5) and our data...
suggest that current clinical management recommendations are relevant across varying screening settings. Absolute risk estimates should be compared across other large screening populations with consideration of age and other population differences.

Disclosure of Potential Conflicts of Interest
J. Cuzick is a consultant/advisory board member for Merck, Hologic, Becton Dickinson, Abbott, and Cepheid. P.E. Castle has received speakers bureau honoraria from Roche and Cepheid. P.E. Castle is a consultant/advisory board member for Roche, Cepheid, Genentech, GE Healthcare, Merck, Inovio, BD, Hologic, ClearPath, Guided Therapeutics, and Teva Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions
Conception and design: J.C. Gage, M. Schiffman, J. Cuzick, C.M. Wheeler Development of methodology: J.C. Gage, L.C. Cheung Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.M. Wheeler Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.C. Gage, W.C. Hunt, M. Schiffman, H.A. Katki, L.C. Cheung, J.C. Gage, O. Myers, P.E. Castle, C.M. Wheeler Writing, review, and/or revision of the manuscript: J.C. Gage, M. Schiffman, H.A. Katki, J. Cuzick, O. Myers, P.E. Castle, C.M. Wheeler Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.C. Gage, O. Myers Study supervision: J.C. Gage

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