Cervical Precancer and Cancer Risk by Human Papillomavirus Status and Cytologic Interpretation: Implications for Risk-Based Management

Philip E. Castle1,2, Shagufta Aslam3, and Catherine Behrens3

Abstract

Background: Cervical cancer risks, estimated by using cervical intraepithelial neoplasia grade 3 (CIN3) or more severe diagnoses (≥CIN3) endpoints, have not been quantified for different combinations of results from currently approved screening methods. Understanding these risks will guide optimal patient management.

Methods: Women aged ≥25 years (n = 7,823) underwent high-risk human papillomavirus (hrHPV) and liquid-based cytology (LBC) testing. Women with hrHPV-positive results and/or abnormal LBC, plus a random subset of hrHPV and LBC negatives, underwent colposcopy; those without ≥CIN2 at baseline were screened annually by LBC and referred to colposcopy for an abnormal LBC (n = 7,392). One- and 3-year ≥CIN3 risks with 95% confidence intervals (95% CI) were calculated for paired hrHPV and LBC (hrHPV/LBC) results.

Results: One-year ≥CIN3 risks ranged from 81.27% (95% CI, 66.02%–90.65%) for HPV16 positive/high-grade to 0.33% (95% CI, 0.18%–0.62%) for hrHPV negative/negative for intraepithelial lesion or malignancy (NILM). One-year ≥CIN3 risk for HPV16/NILM (13.95%; 95% CI, 10.98%–17.58%) was greater than low-grade squamous intraepithelial lesion (LSIL; 7.90%; 95% CI, 5.99%–10.37%; P = 0.002) and similar to hrHPV-positive/LSIL (11.45%; 95% CI, 8.61%–15.07%; P = 0.3). Three-year ≥CIN3 risks for HPV16 positive/LSIL and HPV16/ atypical squamous cells of undetermined significance was 24.79% (95% CI, 16.44%–35.58%) and 24.36% (95% CI, 15.86%–35.50%), respectively, and 0.72% (95% CI, 0.45%–1.14%) for hrHPV negative/NILM.

Conclusions: hrHPV and LBC results stratify cervical cancer risk by more than two orders of magnitude. HPV16-positive women, regardless of the LBC result, warrant immediate colposcopy. Women with concurrent HPV16 and high-grade LBC might consider treatment without a confirmatory biopsy with informed decision-making with their provider.

Impact: These results provide relevant benchmarks for risk-based cervical cancer screening and management. Cancer Epidemiol Biomarkers Prev; 1–5. ©2016 AACR.

Introduction

New cervical cancer screening guidelines and recommendations (1, 2) incorporate high-risk human papillomavirus (hrHPV) testing, thereby taking advantage of the excellent reassurance (1, 2) of high-risk human papillomavirus (hrHPV) and liquid-based cytology (LBC) testing. Women with hrHPV-positive results and/or abnormal LBC, plus a random subset of hrHPV and LBC negatives, underwent colposcopy; those without ≥CIN2 at baseline were screened annually by LBC and referred to colposcopy for an abnormal LBC (n = 7,392). One- and 3-year ≥CIN3 risks with 95% confidence intervals (95% CI) were calculated for paired hrHPV and LBC (hrHPV/LBC) results.

One-year ≥CIN3 risks ranged from 81.27% (95% CI, 66.02%–90.65%) for HPV16 positive/high-grade to 0.33% (95% CI, 0.18%–0.62%) for hrHPV negative/negative for intraepithelial lesion or malignancy (NILM). One-year ≥CIN3 risk for HPV16/NILM (13.95%; 95% CI, 10.98%–17.58%) was greater than low-grade squamous intraepithelial lesion (LSIL; 7.90%; 95% CI, 5.99%–10.37%; P = 0.002) and similar to hrHPV-positive/LSIL (11.45%; 95% CI, 8.61%–15.07%; P = 0.3). Three-year ≥CIN3 risks for HPV16 positive/LSIL and HPV16/ atypical squamous cells of undetermined significance was 24.79% (95% CI, 16.44%–35.58%) and 24.36% (95% CI, 15.86%–35.50%), respectively, and 0.72% (95% CI, 0.45%–1.14%) for hrHPV negative/NILM.

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Materials and Methods

The study methods and description of the population have been reported in detail elsewhere (7). The Institutional Review Boards of all participating clinical sites and institutions approved the study. All participants provided written informed consent.

Briefly, after providing a brief medical history, participants underwent a pelvic exam during which a cervical sample was collected and placed into a PreservCyt vial (Hologic, Inc.). Prior to

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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processing for liquid-based cytology (LBC; ThinPrep; Hologic), a
4-mL PreservCyt aliquot was removed for hrHPV testing using the
analytically sensitive research HPV tests AMPLICOR and LINEAR
ARRAY HPV Genotyping Test as well as the cobas HPV Test (Roche
Molecular Systems). The cobas HPV Test provides three positive/
negative results in three channels: HPV16, HPV18, and a pool of
12 other hrHPV genotypes. A fourth channel provides a read-out
for β-globin as an internal control for the presence of human DNA
(7). LBC results were reported as high-grade squamous intrae-
pithelial lesion (HSIL), atypical squamous cells cannot rule out
HSIL (ASC-H), atypical glandular cells (AGC) of unknown sig-
ificance (AGUS), low-grade squamous intraepithelial lesion
(LSIL), atypical squamous cells of undetermined significance
(ASC-US), and negative for intraepithelial lesion or malignancy
(NILM) (8). All women who had an abnormal LBC [ASC-US or
worse (≥ASC-US)] and/or tested hrHPV positive by AMPLICOR
or LINEAR ARRAY underwent colposcopy with biopsy and, in
some patients, endocervical curettage (ECC) within 12 weeks of
the initial visit; a subgroup of women with both hrHPV and LBC-
negative results was also randomly selected for colposcopy.
Colposcopists and patients were masked to the screening test results
until after the colposcopy visit. A panel of three pathologists
reviewed the biopsies and ECCs masked to patient information
and screening test results (7).

These analyses included 7,823 women, including the 431
women diagnosed with ≥CIN2 at baseline and were exited from
the study. Women who underwent colposcopy in the baseline
phase and did not have ≥CIN2 were eligible for the 3-year follow-
up phase (n = 7,392) as described previously (7). Women in the
follow-up phase were screened annually by cervical cytology and
hrHPV testing as performed by their clinic. Women with abnor-
mal cytology (≥ASC-US) were referred to colposcopy with biopsy
and/or ECC according to the same protocol utilized during the
baseline phase. Women found to have a diagnosis of ≥CIN2 in
follow-up were exited from the study. At year 3, patients were
invited to have an “exit colposcopy” according to the same
protocol at baseline and follow-up. Women who declined the
exit colposcopy (319/4,663, 6.8%) had a cervical specimen col-
lected for LBC and hrHPV testing.

We combined HSIL, ASC-H, or AGC/AGUS into a single
“high-grade” LBC category due to small numbers of each.
Conservatively, we did not calculate the corresponding 3-year
risks for women with high-grade LBC due to the expected low
numbers of these women returning for follow-up, resulting in
unreliable estimates. hrHPV test results were classified positive
and negative for hrHPV and hierarchically according to cancer
risk (9): HPV16 positive, else HPV16 negative and HPV18
positive, else HPV16 and HPV18 negative and positive for the
pool of 12 other hrHPV types, or hrHPV negative. Paired hrHPV
and LBC test results are reported here using a convention of
“hrHPV result/LBC result.”

Cumulative incidence risk (CIR) over 1 or 3 years for the
entire cohort of 7,823 was estimated using Kaplan–Meier
method. That is, CIR represented baseline risk in the 431
women diagnosed with ≥CIN2 at baseline and the cumulative
detection of disease after baseline over 1 and 3 years of follow-
up for the 7,392 women who did not have ≥CIN2 at baseline.
Approximate pointwise confidence intervals (CI) were comput-
ed as in the work of Meeker and Escobar (10). Results were
confirmed using Weibull models as described previously (data
not shown; ref. 11).
Table 1. Cervical Cancer Risk by HPV and Cytology Test Results

<table>
<thead>
<tr>
<th>Baseline LBC result</th>
<th>All</th>
<th>NilM</th>
<th>HsIL</th>
<th>CIN2</th>
<th>CIN3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR-HPV positive</td>
<td>131</td>
<td>177</td>
<td>637</td>
<td>131</td>
<td>131</td>
</tr>
<tr>
<td>HR-HPV negative</td>
<td>304</td>
<td>137</td>
<td>446</td>
<td>304</td>
<td>304</td>
</tr>
<tr>
<td>ASC-US</td>
<td>731</td>
<td>119</td>
<td>612</td>
<td>731</td>
<td>731</td>
</tr>
<tr>
<td>ASC-H</td>
<td>265</td>
<td>78</td>
<td>187</td>
<td>265</td>
<td>265</td>
</tr>
<tr>
<td>AGC</td>
<td>67</td>
<td>11</td>
<td>56</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>NILM</td>
<td>2,562</td>
<td>433</td>
<td>2,525</td>
<td>376</td>
<td>376</td>
</tr>
<tr>
<td>HSIL</td>
<td>67.7%</td>
<td>46.6%</td>
<td>67.7%</td>
<td>46.6%</td>
<td>46.6%</td>
</tr>
<tr>
<td>CIN2</td>
<td>66.6%</td>
<td>48.0%</td>
<td>66.6%</td>
<td>48.0%</td>
<td>48.0%</td>
</tr>
<tr>
<td>CIN3</td>
<td>70.1%</td>
<td>58.0%</td>
<td>70.1%</td>
<td>58.0%</td>
<td>58.0%</td>
</tr>
</tbody>
</table>

NOTE: A total of 7,823 women, those censored at baseline because of HPV negative/NILM, were at the lowest and similar risks, again raising the question of the appropriate follow-up of HPV-negative/NILM women (1, 4, 12).
There were a number of limitations in this study that bear mentioning. First, the aggressive colposcopy protocol likely resulted in earlier identification of CIN2 in CIN2, some of the latter of which might have regressed spontaneously in a year or two (26, 27). For that reason, we relied on CIN2, which is much less regressive, as our primary endpoint. Second, these results need to be replicated given the small numbers and unstable estimates for some of the clinically important combinations of hrHPV testing and cytologic results. Finally, some CIN2 and CIN3 were found by blind biopsy, the clinical significance of which is uncertain. However, a recent study reported that the CIN2/3 biopsies from directed and random biopsies were equally likely to stain positive for p16INK4a (28), which suggests that they are biologically similar.

Finally, as previously suggested (29), there is an increasing complexity in cervical cancer screening and management due to the numerous combinations of clinical results as well as the potential for differences in a priori risks due to screening and vaccination history and age. In addition, new biomarkers may soon be incorporated into routine clinical practice (30). Although there are only five possible clinical actions based on risk bands, screening, increased surveillance, colposcopy, treatment, and exit screening, there are many combinations that can lead to these risks. A clinical algorithm for every clinically meaningful combination of test or diagnostic results is no longer practical. A risk estimation tool, based on the best available population data to estimate risks accurately, is needed in which the patient information that is available can be quickly and easily entered, preferably directly from the electronic medical records database, and the output is the appropriate clinical management. Although decision support tools exist, including one developed by the American Society for Colposcopy and Cervical Pathology, the latter is still based fundamentally on clinical algorithms, and it is unknown how well these tools support the general and/or nonacademic busy practitioner whose starting knowledge of current guidelines may be much less that the academician gynecologist. Thus, an important future goal, in addition to improving upon the risk estimation for more personalized management and improved benefits to harms, is a simple, clear, and direct communication of the recommended clinical actions based on the risk to providers and patients to improve compliance.

Discussion of Potential Conflicts of Interest

P.E. Castle has received speakers bureau honoraria from Cepheid and Roche and is a consultant/advisory board member for Cepheid, ClearPath, GE Healthcare, GenProbe/Hologic, Genentech, Guided Therapeutics, Inovio, Merck, Roche, and Teva. S. Aslam is the principal biostatistician at Roche. C. Behrens is a senior director (Clinical Research) at Roche Molecular Systems and is a consultant/advisory board member for Antiva Biosciences. No other potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: P.E. Castle, C. Behrens

Development of methodology: C. Behrens

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Behrens

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): P.E. Castle, S. Aslam, C. Behrens

Writing, review, and/or revision of the manuscript: P.E. Castle, S. Aslam, C. Behrens

Study supervision: C. Behrens

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NOTE: A total of 7,823 women, those censored at baseline because of CIN2 diagnosis (n = 431) plus those without CIN2 who entered the 3-year follow-up phase of the study (n = 7,392), were included in these analyses. Absolute risks of CIN2 and CIN3 by pairwise combinations of hrHPV and LBC test results for each year was calculated as the proportion of women with >CIN3 or >CIN2 diagnoses, respectively, among the number of women at risk for that year. Calculations for 3-year risks for high-grade LBC for the different category of hrHPV results were not reported because of small numbers of women with high-grade cytology in those HPV categories (5 and 5 for HPV16, 2 and 0 for HPV18, and 11 and 11 for other hrHPV, and 30 and 24 for hrHPV negative for years 2 and 3, respectively) returning after one year.

hsIL, ASC-H, or AGC/typical glandular cells of undetermined significance.

hrHPV testing results were ranked hierarchically according to cancer risk: HPV16 positive, else HPV16 negative and HPV18 positive, else HPV16 and HPV18 negative and positive for the pool of 12 other hrHPV types, or hrHPV negative; ref. 9).

Random sample of all women with hrHPV negative and NILM LBC.

Table 2. Three-year risks of >CIN2 and >CIN3 by pairwise combinations of hrHPV and LBC test results

<table>
<thead>
<tr>
<th>Baseline cobas testing result*</th>
<th>Diagnosis</th>
<th>HSIL*</th>
<th>LSIL</th>
<th>ASC-US</th>
<th>NILM</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>CIR (95% CI)</td>
<td>n</td>
<td>CIR (95% CI)</td>
<td>n</td>
<td>CIR (95% CI)</td>
</tr>
<tr>
<td>All hrHPV positive</td>
<td>433</td>
<td>12.28 (9.28–16.08)</td>
<td>376</td>
<td>12.70 (9.50–16.79)</td>
<td>2562</td>
<td>6.20 (5.28–7.27)</td>
</tr>
<tr>
<td>&gt;CIN3</td>
<td>23.67 (19.66–28.22)</td>
<td>19.80 (15.84–24.46)</td>
<td>10.99 (9.74–12.57)</td>
<td>15.75 (14.50–17.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV18 positive</td>
<td>40.96 (31.02–51.69)</td>
<td>32.86 (23.44–43.89)</td>
<td>23.45 (19.42–28.02)</td>
<td>32.75 (29.11–36.60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;CIN3</td>
<td>32.7 (6.4–29.33)</td>
<td>36</td>
<td>14.00 (3.30–32.12)</td>
<td>189</td>
<td>5.72 (3.05–10.48)</td>
<td>273</td>
</tr>
<tr>
<td>HPV18 positive</td>
<td>17.7 (6.9–12.82)</td>
<td>255</td>
<td>8.71 (5.64–13.22)</td>
<td>1933</td>
<td>3.72 (2.93–4.72)</td>
<td>2536</td>
</tr>
<tr>
<td>HPV16 positive</td>
<td>18.79 (14.53–23.95)</td>
<td>15.88 (11.59–21.37)</td>
<td>8.06 (6.84–9.47)</td>
<td>10.97 (9.73–12.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;CIN2</td>
<td>223</td>
<td>2.01 (0.74–5.31)</td>
<td>967</td>
<td>0.46 (0.17–1.23)</td>
<td>3,073</td>
<td>0.72 (0.45–1.14)</td>
</tr>
<tr>
<td>HPV16 negative</td>
<td>4.35 (2.26–8.19)</td>
<td>1.90 (1.34–3.16)</td>
<td>1.90 (1.44–2.51)</td>
<td>2.21 (1.78–2.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;CIN2</td>
<td>656</td>
<td>8.67 (6.61–12.99)</td>
<td>1,345</td>
<td>3.79 (2.85–5.02)</td>
<td>5,634</td>
<td>3.19 (2.74–3.72)</td>
</tr>
<tr>
<td>HPV18 positive</td>
<td>17.00 (14.17–20.26)</td>
<td>6.84 (5.53–8.43)</td>
<td>6.00 (5.36–6.70)</td>
<td>8.22 (7.60–8.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;CIN2</td>
<td>20.26 (17.08–23.95)</td>
<td>12.09 (9.84–15.19)</td>
<td>17.13 (12.82–22.51)</td>
<td></td>
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