Human Papillomavirus Prevalence in Women Who Have and Have Not Undergone Hysterectomies

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We compared human papillomavirus (HPV) prevalence in an age-stratified random sample of women who have undergone a hysterectomy (WH) (n = 573) with the HPV prevalence in age-matched women with intact cervices (women who have not undergone a hysterectomy [WNH]) (n = 581) participating in a study at Kaiser Permanente in Portland, Oregon. Testing cervicovaginal lavage fluids for >40 HPV genotypes using an MY09/11 L1 consensus primer polymerase chain reaction method, we found no statistical differences in the prevalence of HPV (16% for WNH vs. 13.9% for WH) or carcinogenic HPV (6.5% for WNH vs. 4.5% for WH) between the 2 groups of women. Although WH have a similar prevalence of carcinogenic HPV infection, compared with WNH without a cervix, they have minimal risk of HPV-induced cancer and are unlikely to benefit from HPV testing.

Of the >100 human papillomavirus (HPV) genotypes (hereafter “types”), >40 can infect the lower genital tract, and ~15 carcinogenic HPV types cause virtually all cervical cancer worldwide [1, 2]. HPV is sexually transmitted, but most often infections are transient, becoming undetectable within a year. A fraction of these infections persist; it is persistent cervical carcinogenic HPV infection that is linked to precancer and cancer.

In contrast to cervical cancer, vaginal cancer is rare, but vaginal HPV infection is apparently not. It is difficult to be sure of the site(s) of HPV infection by use of DNA testing given its sensitivity and the possibility of specimen contamination, because the cervix and vagina are apposed. However, we previously observed that HPV is highly prevalent in vaginal specimens from women who have undergone a hysterectomy (WH) [3]. In that report from Guanacaste, Costa Rica (where cervical cancer rates have been high), age-specific prevalences of carcinogenic HPV in vaginal specimens from WH and in cervical specimens from women who have not undergone hysterectomies (WNH) were virtually identical. The age-specific prevalence of noncarcinogenic HPV, especially noncarcinogenic types of the α3/α15 phylogenetic species in women under the age of 45 years, was actually higher in WH than in WNH. There is now further evidence to suggest that these common α3/α15 types preferentially infect the vagina [4].

We collected cervicovaginal/vaginal lavage samples for HPV DNA testing from almost 24,000 women as part of a natural history study of women receiving cytological screening in Portland, Oregon [5]. Approximately 1400 WH enrolled, giving us the opportunity to compare the prevalence of carcinogenic HPV in WH and WNH in this low-risk population.

Participants and methods. From 1 April 1989 to 2 November 1990, 23,702 women receiving routine cytological screening in a prepaid health plan at Kaiser Permanente in Portland were recruited for a cohort study of the natural history of HPV infection [5]. Informed consent was obtained under prevailing institutional review board guidelines at Kaiser and the National Institutes of Health. This cohort of women included 1406 (6%) who had undergone hysterectomy before enrollment; in a subset of 375 women who had their hysterectomy performed at Kaiser, the vast majority (98%) underwent total hysterectomy (i.e., their cervix was removed). The cohort included a demographically representative sample of Portland: Kaiser served approximately one-quarter of the women residing in Portland during this time. For this analysis, age-stratified random samples (16–34 years [n = 50]; 35–44 years [n = 125]; 45–54 years [n = 125]; 55–64 years [n = 125]; ≥65 years [n = 175]) of 600 WH and 600 women with intact cervices (WNH) were selected for HPV testing independent of whether they had answered a questionnaire.

During the cohort study, participants underwent routine pelvic examinations, and a single ethanol-fixed Pap smear for each subject was prepared [5]. Next, the upper genital tract was rinsed with 10 mL of sterile saline [5]. The pooled fluid was collected from the posterior vaginal fornix and processed for HPV testing as described below. Willing subjects completed a...
written, self-administered, 12-question questionnaire about demographic characteristics, smoking habits, contraceptive practices, and parity. WH were more likely to have answered the short questionnaire (95.1%) than WNH (73.0%) (P < .0005), but responding to the questionnaire was not associated with being HPV positive (P = .6).

Lavage specimens were refrigerated within 1 h of collection and transported to a laboratory for processing. A 1-mL aliquot was drawn. The remaining sample was divided in half and centrifuged to pellet cells. Both the 1-mL aliquots and cell pellets were frozen. We selected either frozen 1-mL cell-suspension aliquots (7%) or cell pellets (93%) for HPV testing depending on availability. There was no relationship between hysterectomy status and specimen type (P = 1.0), and specimen type was unrelated to testing positive for HPV DNA (P = A).

Specimens, masked to hysterectomy status, were tested for HPV DNA by an MY09/11 L1 consensus primer polymerase chain reaction (PCR) method, as described elsewhere [6]. Dot blot hybridization of PCR products with HPV type-specific oligonucleotide probes was used for detection of the following HPV types: 2, 6, 11, 13, 16, 18, 26, 31–35, 39, 40, 42–45, 51–59, 61, 62, 64, 66–74, 81–85, 82v, and 89. A specimen was considered to be HPV positive but uncharacterized if it tested positive for HPV DNA by hybridizing with the radiolabeled generic probe mix but was not positive for any type-specific probe. These uncharacterized positives were included in the calculation of overall HPV prevalence as noncarcinogenic HPV infections but were not included in the evaluation of the number of types because there was no way to ascertain the number of “uncharacterized” types present. Forty-six results (4%; (27 for WH and 19 for WNH) were excluded because the human β-globin internal control failed to amplify.

HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were considered to be the primary carcinogenic HPV types for this analysis [2, 7]. We defined HPV risk groups hierarchically according to their a priori associations with cancer [2]: HPV-16, else HPV-16 negative but positive for other carcinogenic HPV types (carcinogenic HPV without HPV-16), else negative for all carcinogenic HPV types but positive for noncarcinogenic HPV types, and else PCR negative.

Prevalence estimates with binomial exact 95% confidence intervals (CIs) were calculated for overall HPV prevalence, for carcinogenic HPV prevalence with and without HPV-16, and for age-group HPV prevalence. Pearson’s χ² and Fisher’s exact statistical tests were used to test for differences in binary outcomes between the 2 groups of women. To compare the HPV prevalence in WH from this population with the HPV prevalence in WH from Guanacaste [3], we calculated the age-standardized HPV prevalence using the distribution by age group of the Costa Rican population of WH. A nonparametric analysis of variance test was used to test for differences in age within the youngest age stratum (<35 years) between the 2 groups of women. We also compared, using Pearson’s χ² and Fisher’s exact statistical tests, the likelihood of cytological abnormality within the whole population of WH versus a matched, age-stratified sample of WNH, the subset of women in both groups who were selected for HPV testing, and the subset of women in both groups who tested HPV positive. Two-tailed P < .05 was considered to be significant.

**Results.** There were no significant differences between the age-stratified random samples of WH and WNH in their income, race, marital status, smoking status, and lifetime number of births. WNH were better educated (P = .03), more likely to attend a clinic for a routine check-up (vs. health problem, birth control, or clinical follow-up request) (P < .0005), and, of course, more likely to use contraception (P < .0005) than WH, but neither education nor contraceptive use was associated with being HPV positive. Although the distribution of clinical sites from which WH and WNH enrolled differed (P = .004), clinical site was not associated with being HPV positive.

Overall, 13.8% (95% CI, 11.1%–16.9%) of WH and 16.0% (95% CI, 13.1%–19.2%) of WNH tested positive for HPV DNA (P = .3) (table 1). There was a nonsignificantly lower prevalence of carcinogenic HPV types in WH (4.5% [95% CI, 3.0%–6.6%]) than in WNH (6.5% [95% CI, 4.7%–8.9%]) (P = .1). There was no significant difference in the prevalence of multiple-type infections (P = .7) or α3/α15 genotypes (P = .6) or by HPV risk group status (HPV-16, else HPV-16 negative but positive for other carcinogenic HPV types, else negative for all carcinogenic HPV types but positive for noncarcinogenic HPV types, and else PCR negative) (P = .4). Exclusion of women who had cancer before the baseline visit (2 WNH and 16 WH) or of women who previously had cervical intraepithelial neoplasia 2 or worse (19 WNH and 27 WH) did not change these findings.

Age standardization, using the age group distribution of the Costa Rican population of WH, revealed that the HPV prevalence and carcinogenic HPV prevalence (excluding HPV-66) in this population of WH (13.8% and 4.2%, respectively) were approximately half of the prevalence observed in the population of WH (28.6% and 9.7%, respectively) from Costa Rica [4]. Similarly, the age-standardized HPV prevalence and carcinogenic HPV prevalence in this population of WNH (14.5% and 4.9%, respectively) was approximately half of the prevalence observed in the population of WNH (23.7% and 9.1%, respectively) from Costa Rica [4].

The HPV prevalence by age group is shown in figure 1. There was no significant difference in the HPV prevalence by age group by hysterectomy status. There was a weak trend toward lower HPV prevalence with age group for both WH (P trend = .03) and WNH (P trend = .05). In the youngest age group (<35 years), there was a nonsignificantly higher prevalence in WNH (30%) than in WH (19%) (P = .2). The numbers of infections
Table 1. Comparison of the prevalence of human papillomavirus (HPV) in an age-stratified random sample of women who have (WH) and have not (WNH) undergone hysterectomies.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>WH (n = 573)</th>
<th>WNH (n = 581)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>79 (13.8)</td>
<td>93 (16.0)</td>
<td>.3</td>
</tr>
<tr>
<td>Negative</td>
<td>494 (86.2)</td>
<td>488 (84.0)</td>
<td></td>
</tr>
<tr>
<td>No. of genotypes</td>
<td></td>
<td></td>
<td>.7</td>
</tr>
<tr>
<td>&gt;2</td>
<td>13 (2.3)</td>
<td>17 (2.9)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>50 (8.7)</td>
<td>55 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Uncharacterized</td>
<td>16 (2.8)</td>
<td>21 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>494 (86.2)</td>
<td>488 (84.0)</td>
<td></td>
</tr>
<tr>
<td>HPV risk group</td>
<td></td>
<td></td>
<td>.4</td>
</tr>
<tr>
<td>HPV-16</td>
<td>8 (1.4)</td>
<td>9 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Carcinogenic without HPV-16(a)</td>
<td>18 (3.1)</td>
<td>29 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Noncarcinogenic</td>
<td>53 (9.2)</td>
<td>55 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>494 (86.2)</td>
<td>488 (84.0)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of women.

\(a\) Excludes HPV type 16 and includes types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.

Unlike HPV analyses in the previous study in a population of women living in Guanacaste [3], we did not observe a higher prevalence of noncarcinogenic HPV infection in WH under the age of 45 than in WNH under the age of 45. In that study, WH were sampled by use of a Dacron swab from the upper vagina, whereas WNH were sampled from the cervical os. In contrast, in the present study, cervicovaginal lavage specimens were collected from both groups and resulted in sampling of the vaginas of WH and both the vaginas and ectocervices of WNH. Thus, the upper vaginas of women in both groups were sampled. We surmise that by performing cervicovaginal lavages on both groups, rather than sampling the cervix in WNH and the upper vaginal vault in WH, controlled for the preferential infection of the vagina by highly prevalent \(\alpha 3/\alpha 15\) types [4].

Cytologic abnormalities were rare in these women, but we also observed that WH were less likely to have any cytologic abnormalities than were WNH, despite the similar prevalence of HPV infection. This is consistent with our previous observation [3]. Given that both groups of women were sampled in an identical fashion and that there was no difference in PCR signal strength (qualitative measure of HPV load [9]) by hysterectomy status (data not shown), it seems likely that the manifestation of cytomorphologic changes is primarily attributable to and a feature of cells from the cervical transformation zone, where the vast majority of HPV-induced cancer occurs.

A strength of the study was that we tested for the same HPV genotypes using the same PCR assay in the same laboratory as we had for the analysis in the Guanacaste study [3]. Thus, we controlled for interassay and interlaboratory differences, allowing us to directly compare HPV prevalence between the 2 stud-

Figure 1. Age group–specific human papillomavirus (HPV) prevalence in women who had (WH) and had not (WNH) undergone hysterectomies. The nos. of WH in each age group were 48 (<35 years), 119 (35–44 years), 118 (45–54 years), 123 (55–64 years), and 165 (≥65 years), after excluding women with invalid polymerase chain reaction (PCR) results. The nos. of WNH in each age group were 47 (<35 years), 118 (35–44 years), 123 (45–54 years), 123 (55–64 years), and 170 (≥65 years), after excluding women with invalid PCR results. Bars indicate binomial exact 95% confidence intervals.
ies of WH. There were several limitations. First, unlike in the Guanacaste study [3], we did not have data on numbers of sex partners in this study (the primary risk factor for testing HPV positive), and, therefore, we could not control for differences in sexual behavior between groups. Second, we also had relatively small numbers of infections that limited our statistical power to look at differences in HPV prevalence for categories of HPV types (e.g., carcinogenic vs. noncarcinogenic and phylogenetic species). Finally, we did not have data on the reasons for hysterectomy.

We conclude that HPV infection is as common in WH as it is in WNH and, not surprisingly, that the HPV prevalence in each is a reflection of the population from which the women are sampled and tested; that is, the HPV prevalence of women, independent of hysterectomy status, reflects the population risk, with the other determinant being the quality of screening. Women who have undergone a total hysterectomy do not have a cervix and are at low risk of HPV-induced cancer of the lower genital tract. Vulvar cancer is much less common than cervical cancer, and vaginal cancer is exceedingly rare [10]. HPV testing, like cytological screening, of WH unnecessarily uses resources without benefit and can potentially harm patients by triggering unnecessary follow-up and anxiety due to a positive test, and, therefore, should not be performed [11, 12].

Acknowledgments

We thank Julie Buckland, John Schussler, and Jared Hellman of Information Management Services, Inc. (Silver Spring, Maryland), for their assistance in data management and analysis.

References