Published in final edited form as:

Gynecol Oncol. 2021 April ; 161(1): 297–303. doi:10.1016/j.ygyno.2021.01.005.

The Relationship of Human Papillomavirus and Cytology Co-Testing Results with Endometrial and Ovarian Cancer Diagnoses

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Disclaimer: The opinions expressed by the authors are their own and this material should not be interpreted as representing the official viewpoint of the U.S. Department of Health and Human Services, the National Institutes of Health or the National Cancer Institute.

Disclosures: Dr. Castle has received HPV tests and assays at a reduced or no cost for research from Roche, Becton Dickinson, Cepheid, and Arbor Vita Corporation. Dr. Strickler has received HPV tests and assays at a reduce or no cost for research from Roche, Becton Dickinson, and Arbor Vita Corporation. Dr. Tergas serves on the Immunomic Therapeutics, Inc, HPV Advisory Board. Drs. Schiffman and Wentzensen have received HPV tests and assays at a reduced or no cost for independent NCI research from Roche, BD, MobileODT, and Qiagen.

Abstract

Background.—To investigate whether routine cervical screening using human papillomavirus (HPV) and cytology co-testing effectively identifies women with endometrial (EC) or ovarian (OvC) cancer.

Methods.—In 2003, Kaiser Permanente Northern California implemented triennial co-testing in women aged ≥30 years. Index screening results (n=2,385,729) were linked to subsequent EC (n=3,434) and OvC (n=1,113) diagnoses from January 1, 2003 to December 31, 2017. EC were categorized as type 1 or 2, and EC and OvC diagnoses were stratified on whether symptoms were present at the time of the co-test. Fractions and absolute risks of EC or OvC of each co-testing result were calculated.

Results.—Most EC (82.18%) and OvC (88.68%) were preceded by a negative HPV and negative cytology co-test. More EC were preceded by atypical squamous cells of undetermined significance (ASC-US) or more severe (ASC-US+) cytology and negative HPV test (n=290) (8.44% of EC) compared to a negative cytology and a positive HPV test (n=31) (0.89% of EC) ($p<0.001$). The absolute risk of any EC diagnosis following ASC-US+ and negative HPV test was 0.48%. Atypical glandular cells (AGC) cytology and a negative HPV result preceded 6.92% of any EC diagnosis, with an absolute risk of 4.02%, but preceded only 1.13% of type 2 EC cases, with an absolute risk of 0.24%, in asymptomatic women. AGC cytology and a negative HPV result preceded 1.44% of OvC, with an absolute risk of 0.28%.

Conclusions.—Abnormal cervical screening tests, even AGC cytology, rarely precedes and poorly predict women with EC or OvC.

Introduction

Currently approved cervical-cancer screening modalities in the U.S. include cervical cytology alone, human papillomavirus (HPV) testing alone (primary HPV testing), and concurrent cytology and HPV testing (“co-testing”) [1]. Globally, cervical-cancer screening is gradually transitioning away from cytology-based testing to HPV-based testing, with many programs electing to use primary HPV testing [1–7]. In the US, HPV testing-based cervical screening is now recommended, either as a co-test [8] or primary HPV testing [8, 9].

Primary HPV testing offers several important advantages over cytology-based screening and co-testing. Compared to cytology, HPV testing is more sensitive, more reliable, has a higher negative predictive value for cervical precancer and cancer, and reduces cervical cancer incidence and mortality [10–12]. Primary HPV testing is less costly and has fewer false-positive results compared to co-testing primarily because of the failure to detect low-risk, HPV-negative mild cytological abnormalities (ASC-US and LSIL) [13]. False-positive results lead to unnecessary clinical follow-up, anxiety, and other downstream consequences for women. The safety conferred by a negative co-test vs. HPV test is minimal, 0.003% (3 per 100,000) lower risk of invasive cervical cancer over 5 years [10], but even these differences are overestimated as a sizable fraction of these cancers are not detected because of screening.

We were interested whether cervical cancer screening might identify women at risk of endometrial and ovarian cancer, and whether a shift from co-testing to primary HPV testing might be less predictive of these cancers. Our *a priori* was that cervical cancer screening by either method would be ineffective for predicting endometrial and ovarian cancer. A recent meta-analysis found that cytology was approximately 50% sensitive for detection of endometrial cancer (EC)[14]. However, many of the studies included in the meta-analysis were limited by: 1) sample size and/or evaluating only a subset of EC; 2) lack of ascertainment of symptoms at the time of cervical-cancer screening; 3) lack of ascertainment of the lead time detection by cytology before diagnosis; 4) differentiating between type 1 and type 2 EC diagnoses, the latter being much more aggressive and lethal than the former [15–19]; and 5) not assessing the fraction of cancers and associated cancer risks for different cytologic results, as measures of sensitivity and risk, respectively. The latter addresses the population effectiveness of using cervical-cancer screening to detect EC and OvC. Based on that meta-analysis [14], some may conclude that cytology plays an important role in EC detection and therefore justifies its continued use in routine cervical-cancer screening, alone or in conjunction with HPV testing as a co-test [20].

To examine further whether cervical-cancer screening may be useful for identifying women with EC or ovarian cancer (OvC), we used a large cervical-cancer screening and outcomes data base developed in collaboration with Kaiser Permanente Northern California to examine the relationship of >2 million cervical-cancer screening results with EC as well as OvC diagnoses. We examined these relationships at the population level, assessing the fraction of cancers and the corresponding absolute and relative risks for these endpoints, and conducted analyses that differentiated between type 1 and 2 EC and between symptomatic vs. asymptomatic EC and OvC at the time of their index cervical-cancer screening result.

Methods

Design, Setting, and Participants

Study population.—Women aged 30 years and older who underwent cervical-cancer screening by cytology and HPV testing (co-testing) within Kaiser Permanente Northern California (KNPC) from January 1, 2003 to December 31, 2017 were identified. For this time period, screening results (n=2,385,729) were linked to EC (n=3,434) and OvC (n=1,113) identified through the KNPC electronic medical records, the KPNC cancer registry, and/or the California Cancer Registry. Laboratory databases and electronic medical records, including reasons for the visit during which the co-testing was performed, and the medical history provided with the Pap requisition, were reviewed to determine if symptoms of EC or OvC were present at the time of the co-test.

The KPNC institutional review board (IRB), National Institutes of Health Office of Human Subjects Research, and Albert Einstein College of Medicine IRB approved the use of these data without patient informed consent.

Cervical Cancer Screening and Management.—Women aged 30 years and older were screened by triennial co-testing as previously described [10]. Two cervical specimens from each woman undergoing co-testing were collected, the first for Pap testing and the

second for high-risk HPV testing using Hybrid Capture 2 (Qiagen, Germantown, MD). Prior to 2009, conventional Pap slides underwent manual review that incorporated the BD Focal Point Slide Profiler (BD Diagnostics, Burlington, NC, USA). Starting in 2009, KPNC transitioned from conventional to liquid-based Pap using BD SurePath (BD Diagnostics, Burlington, NC, USA).

Cytological interpretations were classified according to The Bethesda System [21]: squamous cell cancer or adenocarcinoma, adenocarcinoma *in situ* (AIS), high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells cannot rule out HSIL (ASC-H), atypical glandular cells (AGC), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells of undetermined significance (ASC-US), and negative for intraepithelial lesions and malignancy (NILM). AGC interpretations included the following sub-categorizations: atypical endocervical cells, atypical glandular cells not otherwise specified, atypical endometrial cells, atypical glandular or atypical endocervical cells, favor neoplastic, and endocervical adenocarcinoma *in situ*. Non-cervical cytology results were classified as “Other” and were primarily interpretations of uterine, extra-uterine, or endometrial adenocarcinoma or carcinoma not otherwise specified.

Screen-positive women were managed according to internal Kaiser Guidelines, which were similar to U.S. national guidelines at the time, in which women aged 30 years and older with definite cytological abnormalities (HPV-positive ASC-US, LSIL, or more severe cytological abnormalities) were referred to colposcopy for colposcopically directed biopsies [22–26]. Women with HPV-positive NILM co-test results at KPNC were followed annually with co-testing and were referred to colposcopy if they had cytological abnormalities (from 2003 onward) or second HPV-positive NILM (from 2006 onward) on next co-test.

Analysis

We abstracted the following data from the electronic medical record: EC histology and grade (which were used to classify EC into type 1 or 2), OvC histology and grade, co-testing results, date of co-testing, date of diagnosis of EC or OvC, and whether or not the patient was symptomatic at the time of co-testing (e.g., bleeding, vaginal discharge, and abdominal pain). HPV results were classified as HPV positive (HPV+), HPV negative (HPV−), or missing/not performed. Cytology results were also grouped as ASC-US or more severe (ASC-US+) for all non-negative cytology and as high-grade cytology (HG cytology) for cancer, AIS, HSIL, or AGC cytology. For some analyses, AGC cytologic interpretations were sub-grouped as endometrial (AGC-EM) vs. non-endometrial AGC (AGC-other).

The primary analysis examined the relationship of the co-testing result, which we will denote as the “index” screening result (T_{-1}), that immediately preceded the diagnosis of EC or OvC at time zero (T_0), i.e., there were no other cervical-cancer screening results between the index (T_{-1}) screening result and the diagnoses (T_0).

We conducted a *post-hoc*, more detailed analyses of women with an index cytology of high-grade or other interpretations, the most predictive of EC and OvC, to examine whether there were symptoms at the time of the index text. We focused on this sub-group because it was not feasible to manually review the medical charts for all cases of EC and OvC.

Medical records were reviewed (A.L.) for evidence of symptoms at the time of the index co-test for those with high-grade cytology. In a subset of those women with high-grade cytology and who were concurrently symptomatic, we examined the relationship of the cervical-cancer screening results immediately prior to the index result, which we will denote as the "antecedent" screening result (T_{-2}).

Fractions, absolute risks, relative risks, and etiologic fractions (with 95% confidence intervals (95%CI) of EC or OvC for each cervical-cancer screening result were calculated. SAS version (Cary, NC, USA) and STATA version 16.0 (College Station, TX, USA). Logistic regression was used to calculate odds ratio (OR) to assess the independent association of HPV testing results, AGC-EM vs. AGC-other, and age (<50 years vs. 50 years and older) at the time of the index co-test and EC. A two-sided p value of <0.05 was considered statistically significant.

RESULTS

For the study period, there were 2,385,729 index screening results, 3,434 EC diagnosed, and 1,055 OvC diagnosed. The mean, median, interquartile range, and range of age of women at time of the index screening were 45.4, 45, 37–53, and 30–98 years, respectively. The mean, median, interquartile range, and range of age of women at time of the EC diagnosis were 60.9, 61, 55–67, and 30–91 years, respectively. The mean, median, interquartile range, and range of age at time of the OvC diagnosis were 56.7, 57, 49–65, and 30–89 years, respectively.

Endometrial Cancer

Of the 3,434 EC diagnosed, 51.05% were grade 1 endometrioid histology (type 1 EC); 28.02% of all EC diagnosed were classified as type 2 EC (e.g., serous, clear cells, mixed mullerian). The mean, median, and range of time between the index co-test and ED diagnoses were 904, 469, and 1–5,347 days, respectively.

Table 1 and Supplemental Table 1 show the relationship of index cervical-cancer screening results (cytology and HPV) (T_{-1}), the number of EC associated with each combination of screening result, and the time between EC diagnosis and the index co-test (T_0 —T_{-1}). Most EC were preceded by negative cytology (N=2,982, 86.84% of EC), the majority of which also tested HPV negative (negative co-test) (N=2,822, 82.18% of EC). Fraction and absolute risk of EC for ASC-US+ cytology were 11.01% and 0.20% (95%CI=0.18–0.22%), respectively. Corresponding mean, median, and range of times between the index co-test and diagnoses were 136, 51, and 3–3,094 days, respectively. The fraction and absolute risk of EC associated with a positive HPV result were 2.27% and 0.04% (95%CI=0.03–0.04%), respectively. Mean, median, and range of times between the index co-test and diagnoses were 280, 143, and 10–3,116 days, respectively. Etiologic fractions for EC for any co-test result ranged between 0.06–0.08.

Among those with positive screening result (ASC-US+ and/or HPV positive), some of the greatest fractions of EC were associated with ASC-US+/HPV− (8.44%), HG cytology/HPV− (7.31%), and AGC/HPV− (6.99%). Corresponding absolute risks of EC

were 0.48% (95%CI=0.42–0.53%) for ASC-US+/HPV−, 2.99% (95%=2.64–3.38%) (1 in 208 HG cytology/HPV−) for HG cytology/HPV−, and 4.15% (95%CI=3.65–4.70%) for AGC/HPV−. Relative risks of EC were 3.06 (95%CI=2.72–3.46) for ASC-US+/HPV−, 19.25 (95%CI=16.95–21.86) for HG cytology/HPV−, and 26.73 (95%CI=23.49–30.42) for AGC/HPV− (vs. a negative co-test). Notably, the fraction and absolute risk of EC for other (non-cervical) cytology results, which were interpreted predominately endometrial cancer cytology, were 1.57% and 36.00% (95%CI=28.33–44.23%), respectively.

Table 2 shows the fraction and absolute risk for EC for index co-testing results that include a high-grade cytology, restricted to those women who were asymptomatic at the time of the co-test, and stratified by type 1 or 2 cases. There were no appreciable differences in the fraction and risk of asymptomatic type 1 vs. type 2 for any index co-testing result. The fraction and absolute risk of asymptomatic EC were highest for HG cytology/HPV− (1.82% and 0.51%, respectively, for type 1; 1.78% and 0.20%, respectively, for type 2) and AGC/HPV− (1.78% and 0.73%, respectively, for type 1; 1.13% and 0.24%, respectively, for type 2).

Relationships of index HPV testing results, AGC subcategories, and age with EC diagnoses are shown in Table 3. Women who were HPV negative, had AGC-EM, and were 50 years and older (n=435) had a 14.02% absolute risk of EC but only accounted for 1.78% of EC in this cohort. By comparison, those who did not have any of those markers (i.e., HPV positive, AGC-other, and <50 years old) (n=1,494) had a 0.26% absolute risk of EC. In a logistic regression model, testing HPV negative (vs. positive) (OR=6.6, 95%CI=3.2–13.8), having a AGC-EM cytology (vs. other AGC) (OR=2.3, 95%CI=1.7–3.0), and being age 50 years and older (vs. <50 years) (OR=6.7, 95%CI=4.8–9.4) were all independently associated with being diagnosed with EC.

Table 4 shows antecedent (T_{-2}) screening result for 171 of the 361 EC that were confirmed to be already symptomatic at the time of an index (T_{-1}) screening result with high-grade or non-cervical cytology. The time between the index co-test and diagnosis for these cases had a range of 9–505 days, a mean of 63 days, and a median of 40 days. The time between the antecedent co-test and diagnosis for these cases had a range 83–3,780 days, a mean of 1,306 days, and a median of 1,177 days. The time between the antecedent co-test and index co-test for these cases had a range of 46–3,737 days, a mean of 1,244, and a median of 1,114 days. Most (97.66%) had antecedent (T_{-2}) negative cytology and 92.40% had a negative co-test. There were no appreciable differences in the distribution of antecedent co-testing results between type 1 and 2 cases (p=0.48).

Ovarian Cancer

Table 5 and Supplemental Table 2 shows the relationship of cervical-cancer screening results (cytology and HPV), the number of OvC associated with each combination of screening result, and the time between the cervical-cancer screening and OvC diagnoses. Similar to EC results, the majority of OvC (N=1,055, 94.79% of all OvC) were preceded by negative cytology, the majority of which also tested HPV negative (negative co-test) (N=1,021, 91.73% of all OvC). The mean, median and range of time between the index co-test and the OvC diagnoses were 933, 567, and 2–5,544 days, respectively.

The fraction of cancers and risk of OvC associated with non-negative cytology (ASC-US+) were 4.85% and 0.03% (95%CI=0.02–0.04%), respectively. The fraction of cancers and risk of OvC associated with a positive HPV test were 3.41% and 0.02% (95%CI=0.01–0.02%), respectively.

Etiologic fractions of OvC for any co-test result were ≤0.01. For specific combination of index co-testing results, some of the greatest fractions of OvC were associated with ASC-US+/HPV− (2.70%), HG cytology/HPV− (1.53%), and AGC/HPV− (1.44%). Corresponding absolute risks for OvC of those co-testing results were 0.05% (95%CI=0.03–0.07%), 0.20% (95%CI=0.12–0.32%), and 0.28% (95%CI=0.16–0.45%), respectively. Relative risks of OvC were 0.91 (95%CI=0.63–1.30) for ASC-US+/HPV−, 3.73 (95%CI=2.31–6.02) for HG cytology/HPV−, and 5.10 (95%CI=3.11–8.34) for AGC/HPV−. Thirty-one of 32 (97.06%) cases of OvC preceded by a co-test of ASC-US+ and negative or missing/not performed HPV results were already symptomatic at the time of co-testing for cervical-cancer screening.

DISCUSSION

This long-term retrospective, observational cohort study, based in a large managed care organization, of more than 2 million co-tests found that cervical cytology was very insensitive and non-specific for asymptomatic endometrial or ovarian cancer. ASC-US+/HPV− was the most sensitive “marker” for EC but was associated with only ~1 in 12 EC, with a corresponding absolute risk of approximately 1 EC diagnosed in 200 women with ASC-US+/HPV−. By comparison, AGC/HPV− was a more specific marker for EC but as only associated with ~1 in 14 EC, with a corresponding absolute risk of approximately 1 EC diagnosed in 25 women with AGC/HPV−. However, less than 15% of these EC cases were type 2 EC, the lethal type of EC, and were detected before documented symptoms. *Therefore, at best, 1 asymptomatic, type 2 EC in >1,333 women with ASC-US+/HPV− and 1 in >166 women with AGC/HPV− would be diagnosed, and most EC would not be preceded by these indications.* Finally, most cervical-cancer screening occurs in women under the age of 65 years while many EC are diagnosed at older ages, since the median age of endometrial cancer is ~60 years. Thus, the fraction of EC diagnosed as presented in these analyses is overestimated since many women diagnosed with EC no longer are undergoing routine cervical-cancer screening.

A recent meta-analysis [14] reported a 45% sensitivity of non-negative cytology for EC, much greater than observed in this study. Yet, in most of the studies included in this meta-analysis, cytology was performed after diagnosis or the temporality between cytology and diagnosis was unknown. Moreover, these studies did not account for the presence of symptoms. Conversely, in the current analysis of primarily in routine co-testing (vs. taken at the time of diagnosis or symptoms), we found the sensitivity of all combinations of cytology and HPV testing to be much lower, and the sensitivity of ASC-US+ to be approximately 11% (378 of 3434), in routine practice was much lower when done a mean of ~4 months prior to diagnosis. Of the few studies [27–29] in which the cytology was done before diagnosis and the time interval was reported, the sensitivity for EC was approximately 40% for ASC-US+ done within 6 months of diagnosis.

Many of these studies did not account for the presence of symptoms at the time of the cytology. Given that most of the studies evaluated cytologic detection of EC near or at the time of diagnosis, most were likely already symptomatic. Of those that were not, a few months of lead-time detection may not offer significant benefits in terms of down-staging of the cancer and corresponding reduced morbidity and mortality. Of note, the frequency of cervical-cancer screening is not every 6 months or even 12 months, even using cytology alone, but every 3 to 5 years around the world [1–7], optimizing benefits vs. harms of cervical-cancer screening; in other words, the actual sensitivity of cytology to detect EC in asymptomatic women at routine CCS practice is expected to be much lower still.

The aforementioned meta-analysis [14] also stratified on endometrioid vs. non-endometrioid EC/advanced cancers, essentially for type 1 and 2 EC [15–19], respectively, and found that sensitivity of cytology for EC was higher for the latter. Given the limitations of the studies that contributed to the meta-analysis, this greater sensitivity for EC may simply reflect the more aggressive nature of type 2, resulting in more sloughing of abnormal cells into the reproductive tract.

There have been many reports examining the relationship of AGC cytology with subsequent diagnoses of EC, and in some reports, OvCs [30–41]. These studies, like ours, found AGC, especially AGC/HPV−, strongly predictive of EC, but only occurs in 0.24% of screens. The average of the reported risks of EC for AGC was around 5% but ranged from approximately 1–2% [30, 31] to more than 10% [32, 39]. These studies typically did not account for or report on the time between AGC and the subsequent diagnosis of EC. In our study, the mean time between AGC and EC diagnoses was only ~3 months, which even for asymptomatic women may not afford enough lead time to improve clinical outcomes.

A number of studies found that the risk of EC for AGC for EC was influenced by HPV status (negative vs. HPV positive; [31, 32, 36, 41]), age (50+ vs. <50 years; [30, 34–37, 39]), and/or sub-categories of AGC (AGC-EM vs. other AGC) [34–37, 39] but few have looked at all these concurrently. Here, in the largest study to date, we found all three independently were associated with being diagnosed with EC. Yet, the vast majority were symptomatic at the time of the index co-test, and only a small fraction of EC was identified in a relatively highly specific (i.e., with high positive predictive value) manner.

As cervical-cancer screening shifts from cytology alone to HPV testing-based screening, the question remains whether there is an added benefit to co-testing vs. HPV testing alone for earlier detection of EC to prevent related mortality. We cannot answer this question directly as all these data were not used to inform clinical interventions. At KPNC, endometrial biopsy is recommended only for women with AGC if they are aged 35 years and older or younger than 35 and have concurrent symptoms or deemed to be at high risk. Similar guidelines are likely followed in other practices. We speculate that the reduction in EC mortality is minimal when considering the small fraction of asymptomatic women that have AGC (or any abnormality) sufficiently in advance of a type 2 EC diagnosis leading to detection of a precursor, endometrial hyperplasia, or down-staging of the cancer to prevent incidence of aggressive EC or mortality, respectively.

Several other screening and diagnostic approaches may provide diagnostic utility for detection of EC or OvC. Post-menopausal bleeding is sensitive albeit not specific for EC [42]. Cross-sectional genetic analyses of cervical specimens have been shown to pick up a high percentage of EC and a significant fraction of OvC [43, 44], and cross-sectional somatic mutation analyses of blood ("liquid biopsy") has been evaluated for detection of OvC [43]. Image analysis and computer algorithms of cytologic specimens has shown reasonable performance for EC [45]; further advances in artificial intelligence-based analysis, including deep learning, may further this approach still. Yet, for any approach, it will be necessary to demonstrate either lead-time detection and down-staging of EC or OvC or detection of endometrial hyperplasia with invasive potential to provide true clinical benefit and justify their use for screening on a population level. To date, none have.

We noted several limitations of these analyses. First, ~10% of the screening results abstracted from the electronic medical records did not have a corresponding HPV test. Approximately one quarter of the missing/non-performed results were women undergoing screening in 2003, when HPV testing was being implemented in a stepwise manner and therefore not immediately available to all women aged 30 years and older. We speculate that some of these screens may have been done as cytology-only screens in women suspected of having EC or OvC. However, there is no reliable way to discern those results from routine screening with missing/not-performed HPV results and those cytology-only diagnostics. The interval between the index test and the diagnosis appear similar by HPV status (missing/not-performed vs. negative vs. positive result) (data not shown), which suggests that most data are from women attending routine cervical-cancer screening practice rather than rather than targeted cytology testing of those suspected of having EC. Second, because this was routine practice vs. a clinical trial or a randomized clinical trial, we could not assess the impact of systematic intervention-based co-testing results. At KPNC, only women with an AGC cytology who were 35 years and older, or younger than 35 years and have concurrent symptoms or deemed to be at high risk, were recommended for routine endometrial biopsy, too small a fraction of the cases of EC to measure a difference in mortality, even if we had a suitable comparison group. Finally, self-reported symptom data were extracted from medical records and not systematically collected, which likely led to under-ascertainment.

We cannot assess whether systematically intervening on women with cytologic abnormalities would have led to downstaging of EC since that was not the clinical algorithm at KPNC to do so, with the noted exception of AGC. Therefore, we limited largely to assessing the temporal relationships. Of note, we did not observe a significant difference in stage distribution between women who had negative and AGC cytology and diagnosed with endometrioid adenocarcinoma (p=0.20) or serous adenocarcinoma (p=0.59) (data not shown), the two most common histologic types of EC diagnosed at KPNC.

In conclusion, while we cannot rule out that co-testing might lead to additional diagnostic workup among asymptomatic women at risk of a lethal EC that primary HPV testing would not, the numerical and fractional differences between co-testing and primary HPV testing were very small. Further, an improvement in mortality, or at least a stage shift, in context of potential harms for workup of cytology-positive women, would need to be shown to establish a benefit of co-testing for other gynecological cancer sites. Thus, taking all the

evidence together, co-testing may offer little added benefit in terms of the detection of, or safety against, any gynecological cancer over primary HPV testing, as reflected in the recent American Cancer Society recommendations for primary HPV testing for cervical-cancer screening [9].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support: B.B. was supported by grant number T32CA09168 from NCI/NIH.

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- More than 80% of endometrial cancers were preceded by a negative HPV and cytology co-test.
- More than 80% of ovarian cancers were preceded by a negative HPV and cytology co-test.
- Abnormal cytology, even atypical glandular cells, is poorly predictive of endometrial and ovarian cancer.

Table 1.

Relationship of cervical screening results and endometrial cancer diagnoses of any histology or grade and the time interval statistics between the two.

Cytology	HPV	N (Tests)	N (Cancers)	% of Cancers	Risk	95%CI
Missing	Any[¥]	15,769	20	0.58%	0.13%	0.08–0.20%
NILM	Any	2,180,297	2,982	86.84%	0.14%	0.13–0.14%
Other[†]	Any	150	54	1.57%	36.00%	28.33–44.23%
ASC-US	Any	109,551	56	1.63%	0.05%	0.04–0.07%
LSIL	Any	53,813	15	0.44%	0.03%	0.02–0.05%
ASC-H	Any	9,783	12	0.35%	0.12%	0.06–0.21%
AGC	Any	8,638	261	7.60%	3.02%	2.67–3.40%
HSIL/AIS	Any	7,570	9	0.26%	0.12%	0.05–0.23%
SCC	Any	158	25	0.73%	15.82%	10.51–22.47%
HG cytology[‡]	Any	26,149	307	8.94%	1.17%	1.05–1.31%
HG cytology[‡] or Other[†]	Any	26,299	361	10.51%	13.72%	12.36–15.21%
ASC-US+[§]	Any	189,513	378	11.01%	0.20%	0.18–0.22%
ASC-US+[§] or Other[†]	Any	189,663	432	12.68%	0.23%	0.21–0.25%
AGC	Negative	5,782	240	6.99%	4.15%	3.65–4.70%
HG cytology[‡]	Negative	8,398	251	7.31%	2.99%	2.64–3.38%
HG cytology[‡] or Other[†]	Negative	8,501	299	8.71%	3.51%	3.14–3.93%
ASC-US+[§]	Negative	60,951	290	8.44%	0.48%	0.42–0.53%
ASC-US+[§] or Other[†]	Negative	61,054	338	9.84%	5.54%	4.96–6.16%
NILM	Positive	105,879	30	0.87%	0.03%	0.02–0.04%
Any	Missing	270,915	177	5.15%	0.07%	0.06–0.08%
Any	Negative	1,892,808	3,179	92.57%	0.17%	0.16–0.17%
Any	Positive	222,006	78	2.27%	0.04%	0.03–0.04%
Any	Any	2,385,729	3,434	100.00%	0.14%	0.14–0.15%

Abbreviations: SCC, squamous cell carcinoma; HSIL, high-grade squamous intraepithelial lesion; AIS, adenocarcinoma *in situ*; AGC, atypical glandular cells; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy; HG = high-grade cytology

[*] One-sided, 97.5% confidence interval

[**] Time between co-test and endometrial cancer diagnosis in days

[†] Other=interpretations of non-cervical changes, primarily of uterine, extra-uterine, or endometrial adenocarcinoma or carcinoma not otherwise specified

[‡] ASC-H, AGC, HSIL/AIS, and SCC (excludes Other)

[§] All non-normal cervical cytology (excludes Other)

[¥] Excluding HPV missing

Table 2.

Relationship of cervical screening results and endometrial cancer diagnoses for 58 women who had high-grade or other cytology who had documented symptoms *after* the index co-test in their electronic medical records i.e., they were asymptomatic at the time of the index co-test.

		Type 1			Type 2		
Cytology	**HPV**	**% of type 1 endometrial cancers**	**Risk**	**95%CI**	**% of type 2 endometrial cancers**	**Risk**	**95%CI**
AGC	Positive	0.04%	0.05%	0.00–0.28%	0.21%	0.10%	0.01–0.36%
AGC	Negative	1.78%	0.73%	0.52–0.98%	1.13%	0.24%	0.13–0.41%
AGC	Missing	0.00%	0.00%	0.00–0.43%*	0.00%	0.00%	0.00–0.43%*
AGC	Any	1.82%	0.50%	0.36–0.67%	1.33%	0.19%	0.11–0.30%
ASC-H	Positive	0.08%	0.03%	0.00–0.10%	0.00%	0.00%	0.00–0.05%*
ASC-H	Negative	0.04%	0.05%	0.00–26%	0.21%	0.09%	0.01–0.33%
ASC-H	Missing	0.00%	0.00%	0.00–0.68%*	0.00%	0.00%	0.00–0.68%*
ASC-H	Any	0.13%	0.03%	0.00–0.09%	0.21%	0.02%	0.00–0.07%
HSIL/AIS	Positive	0.13%	0.05%	0.01–0.14%	0.21%	0.03%	0.00–0.11%
HSIL/AIS	Negative	0.00%	0.00%	0.00–0.83%*	0.10%	0.23%	0.01–1.25%
HSIL/AIS	Missing	0.00%	0.00%	0.00–0.58%*	0.00%	0.00%	0.00–0.58%*
HSIL/AIS	Any	0.13%	0.04%	0.01–0.12%	0.31%	0.04%	0.00–0.12%
Other	Positive	0.00%	0.00%	0.00–45.93%*	0.00%	0.00%	0.00–45.93%*
Other	Negative	0.00%	0.00%	0.00–3.52%*	0.42%	3.88%	1.07–9.65%
Other	Missing	0.00%	0.00%	0.00–8.60%*	0.00%	0.00%	0.00–8.60%*
Other	Any	0.00%	0.00%	0.00–2.43%*	0.42%	2.67%	0.73–6.69%
SCC	Positive	0.00%	0.00%	0.00–7.25%*	0.00%	0.00%	0.00–7.25%*
SCC	Negative	0.00%	0.00%	0.00–45.93%*	0.00%	0.00%	0.00–45.93%*
SCC	Missing	0.04%	0.97%	0.02–5.29%	0.42%	3.88%	1.07–9.65%
SCC	Any	0.04%	0.63%	0.02–3.48%	0.42%	2.53%	0.69–6.35%
HG	Positive	0.25%	0.04%	0.01–0.08%	0.42%	0.03%	0.01–0.07%
HG	Negative	1.82%	0.51%	0.37–0.69%	1.78%	0.20%	0.12–0.32%
HG	Missing	0.04%	0.05%	0.00–0.26%	0.42%	0.19%	0.05–0.48%

		Type 1			Type 2		
Cytology	**HPV**	**% of type 1 endometrial cancers**	**Risk**	**95%CI**	**% of type 2 endometrial cancers**	**Risk**	**95%CI**
HG	Any	2.12%	0.19%	0.14–0.25%	2.62%	0.10%	0.06–0.14%

Abbreviations: SCC, squamous cell carcinoma; HSIL, high-grade squamous intraepithelial lesion; AIS, adenocarcinoma *in situ*; AGC, atypical glandular cells; HG = high-grade cytology

*One-sided, 97.5% confidence interval

**At time of the antecedent co-test

†Other= interpretations of non-cervical changes, primarily of uterine, extra-uterine, or endometrial adenocarcinoma or carcinoma not otherwise specified

‡ASC-H, AGC, HSIL/AIS, and SCC (excludes Other)

Table 3.

Relationships of the human papillomavirus (HPV) testing result, atypical glandular cells (AGC) subcategory (AGC favors endometrial [AGC-EM]) vs. AGC other), and age (<50 years vs. 50 years and older [≥50]) at the time of the index HPV and cytology co-testing with endometrial cancer.

HPV Status	AGC Pap	Age (Years)	N	N(Cases)	% of Cancers**	Risk
HPV−	AGC-EM	<50	428	9	0.26%	2.10%
		≥50	435	61	1.78%	14.02%
		All	863	70	2.04%	8.11%
	AGC-Other	<50	2,862	31	0.90%	1.08%
		≥50	2,058	139	4.05%	6.75%
		All	4,920	170	4.95%	3.46%
	Any AGC	<50	27	0	0.00%	0.00%
		≥50	16	2	0.06%	12.50%
		All	43	2	0.06%	4.65%
HPV+	AGC-EM	<50	1,494	3	0.09%	0.20%
		≥50	468	3	0.09%	0.64%
		All	1,962	6	0.17%	0.31%
	AGC-Other	<50	455	9	0.26%	1.98%
		≥50	451	63	1.83%	13.97%
		All	906	72	2.10%	7.95%
	Any AGC	<50	4,356	34	0.99%	0.78%
		≥50	2,526	142	4.14%	5.62%
		All	6,882	176	5.13%	2.56%
Any HPV Result*	AGC-EM	<50	4,811	43	1.25%	0.89%
		≥50	2,977	205	5.97%	6.89%
		All	7,788	248	7.22%	3.18%
	AGC-Other	<50	428	9	0.26%	2.10%
		≥50	435	61	1.78%	14.02%
		All	863	70	2.04%	8.11%
	Any AGC	<50	2,862	31	0.90%	1.08%
		≥50	2,058	139	4.05%	6.75%
		All	4,920	170	4.95%	3.46%

*Does not include missing HPV results

**fraction of all endometrial cancers (n=3,434) in this cohort

Table 4.

Antecedent (T_{-2}) cytology and HPV co-testing results that occurred before symptoms for 171 cases of endometrial cancer diagnosed (T_0) with an index (T_{-1}) co-test result of high-grade cytology or non-cervical (other) cytology that occurred after symptoms. The mean, median, and range of times between the index (T_{-1}) co-test and EC diagnosis (T_0) for these cases were 9–505, 63, and 40 days, respectively. The mean, median, and range of times between the antecedent (T_{-2}) co-test and EC diagnosis (T_0) were 83–3,780, 1,306, and 1,177 days, respectively. The mean, median, and range of times between the antecedent (T_{-2}) co-test and index (T_{-1}) co-test were 46–3,737, 1,244, and 1,114 days, respectively.

Co-Testing Results		Type 1		Type 2		Total	
Cytology	**HPV**	**N**	**%**	**N**	**%**	**N**	**%**
NILM	Missing	4	3.74%	2	3.13%	6	3.51%
NILM	Negative	97	90.64%	61	95.31%	158	92.40%
ASC-US	Negative	2	1.87%	0	0.00%	2	1.17%
AGC	Negative	0	0.00%	1	1.56%	1	0.58%
NILM	Positive	3	2.80%	0	0.00%	3	1.75%
LSIL	Positive	1	0.93%	0	0.00%	1	0.58%
Total		107	100.0%	64	100.0%	171	100.0%

Table 5.

Relationship of cervical screening results and ovarian cancer diagnoses of any histology or grade and the time interval statistics between the two.

Cytology	HPV	N (Tests)	N (Cancers)	% of Cancers	Risk	95%CI
Missing	Any[¥]	15,769	2	0.18%	0.01%	0.00–0.05%
NILM	Any	2,180,297	1,055	94.79%	0.05%	0.05–0.05%
Other [†]	Any	150	2	0.18%	1.33%	0.16–4.73%
ASC-US	Any	109,551	20	1.80%	0.02%	0.01–0.03%
LSIL	Any	53,813	10	0.90%	0.02%	0.01–0.03%
ASC-H	Any	9,783	1	0.09%	0.01%	0.00–0.06%
AGC	Any	8,638	17	1.53%	0.20%	0.11–0.31%
HSIL/AIS	Any	7,570	4	0.36%	0.05%	0.01–0.14%
SCC	Any	158	2	0.18%	1.27%	0.15–4.50%
HG cytology[‡]	Any	26,149	24	2.16%	0.09%	0.06–0.14%
HG cytology[‡] or Other[†]	Any	26,299	26	2.34%	0.10%	0.06–0.14%
ASC-US+[§]	Any	189,513	54	4.85%	0.03%	0.02–0.04%
ASC-US+[§] or Other[†]	Any	189,663	56	5.03%	0.03%	0.02–0.04%
AGC	Negative	5,782	16	1.44%	0.28%	0.16–0.45%
HG cytology[‡]	Negative	8,398	17	1.53%	0.20%	0.12–0.32%
HG cytology[‡] or Other[†]	Negative	8,501	19	1.71%	0.22%	0.13–0.35%
ASC-US+[§]	Negative	60,951	30	2.70%	0.05%	0.03–0.07%
ASC-US+[§] or Other[†]	Negative	61,054	32	2.88%	0.05%	0.04–0.07%
NILM	Positive	105,879	16	1.44%	0.02%	0.01–0.02%
Any	Missing	270,915	54	4.85%	0.02%	0.01–0.03%
Any	Negative	1,892,808	1,021	91.73%	0.05%	0.05–0.06%
Any	Positive	222,006	38	3.41%	0.02%	0.01–0.02%
Any	Any	2,385,729	1,113	100.00%	0.05%	0.04–0.05%

Abbreviations: SCC, squamous cell carcinoma; HSIL, high-grade squamous intraepithelial lesion; AIS, adenocarcinoma *in situ*; AGC, atypical glandular cells; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy; HG = high-grade cytology

[*] One-sided, 97.5% confidence interval

[**] Time between co-test and endometrial cancer diagnosis in days

[†] Other=interpretations of non-cervical changes, primarily of uterine, extra-uterine, or endometrial adenocarcinoma or carcinoma not otherwise specified

[‡] ASC-H, AGC, HSIL/AIS, and SCC (excludes Other)

[§] All non-normal cytology (excludes Other)

[¥] Excluding HPV missing