HHS Public Access

Author manuscript

Gynecol Oncol. Author manuscript; available in PMC 2018 September 01.

Published in final edited form as:

Gynecol Oncol. 2017 September ; 146(3): 546–553. doi:10.1016/j.ygyno.2017.06.003.

Why does cervical cancer occur in a state-of-the-art screening program?

Philip E. Castle[1,*], **Walter K. Kinney**[2], **Li C. Cheung**[3], **Julia C. Gage**[3], **Barbara Fetterman**[2], **Nancy E. Poitras**[2], **Thomas S. Lorey**[2], **Nicolas Wentzensen**[3], **Brian Befano**[4], **John Schussler**[4], **Hormuzd A. Katki**[3], and **Mark Schiffman**[3]

[1]Albert Einstein College of Medicine, Bronx, NY, USA

[2]Regional Laboratory, The Permanente Medical Group, Oakland, CA, USA

[3]Division of Cancer Epidemiology and Genetics, NCI, Bethesda, MD, USA

[4]IMS, Calverton, MD, USA

Abstract

Background—The goal of cervical screening is to detect and treat precancers before some become cancer. We wanted to understand why, despite state-of-the-art methods, cervical cancers occur related to programmatic performance at Kaiser Permanente Northern California (KPNC), where >1,000,000 women aged ≥30 years have undergone cervical cancer screening by triennial HPV and cytology cotesting since 2003.

Methods—We reviewed clinical histories preceding cervical cancer diagnoses to assign "causes" of cancer. We calculated surrogate measures of programmatic effectiveness (precancers/(precancers and cancers)) and diagnostic yield (precancers and cancers per 1,000 cotests), overall and by age at cotest (30–39, 40–49, and ≥50 years).

Results—Cancer was rare and found mainly in a localized (treatable) stage. Of 623 cervical cancers with at least one preceding or concurrent cotest, 360 (57.8%) were judged to be prevalent (diagnosed at a localized stage within one year or regional/distant stage within two years of the first cotest). Non-compliance with recommended screening and management preceded 9.0% of all cancers. False-negative cotests/sampling errors (HPV and cytology negative), false-negative histologic diagnoses, and treatment failures preceded 11.2%, 9.0%, and 4.3%, respectively, of all cancers. There was significant heterogeneity in the causes of cancer by histologic category ($p<0.001$ for all; $p=0.002$ excluding prevalent cases). Programmatic effectiveness (95.3%) and

[*]Correspondence: 1300 Morris Park Avenue, Belfer Building, Room 1308C, Bronx, NY, 10461, USA. Phone: (703) 772-0611. castle.philip@gmail.com.

Disclosures: The authors have no relationships to disclose.

Conflict of Interest Statement

The NCI has received received cervical cancer screening assays in-kind or at reduced cost from BD, Cepheid, Hologic, and Roche. Dr. Castle has Dr. Castle has received HPV tests and testing for research at a reduced or no cost from Qiagen, Roche, MTM, and Norchip. No other author reports a conflict of interest.

diagnostic yield were greater for squamous cell versus adenocarcinoma histology ($p<0.0001$) and both decreased with older ages ($p_{trend}<0.0001$).

Conclusions—A state-of-the-art intensive screening program results in very few cervical cancers, most of which are detected early by screening. Screening may become less efficient at older ages.

Introduction

U.S. cervical cancer screening guidelines have changed over the last dozen years with the introduction of clinical testing for high-risk human papillomavirus (HPV) types, those that cause virtually all cervical cancers and their immediate precursor lesions [1], into routine practice. HPV testing has superior sensitivity compared with cytology (cytology tests) for screening and secondary prevention of cervical cancer via detection and treatment of precursor lesions [2, 3]. In January 2003, just prior to U.S. FDA approval of cotesting in mid-2003 [4] and interim guidelines [5] in 2004, Kaiser Permanente Northern California (KPNC), a large integrated health care organization, introduced 3-year cotesting in women aged 30 years and older. KPNC has now screened over 1 million women by cotesting; to our knowledge, this is the most extensive experience of clinical HPV testing in the world.

Internationally, the optimal cervical screening interval and choice of testing method remain controversial [6–10]. Most concerns have centered on the specificity of HPV testing, and the proper management of HPV-positive women. Accumulated evidence regarding cervical screening tests and program strategies is currently under re-review by the U.S. Preventive Services Task Force [11]. To optimize guidelines development and dissemination, we have undertaken a set of analyses using data from the KPNC program to examine the programmatic performance of 3-year cotesting. Here, we examine the reasons why some cervical cancers may still occur despite a concerted, high-quality program and describe the overall performance of the program to detect precancer prior to becoming invasive cancer.

Methods

Population

The cohort study within KPNC has been described previously [12]. From January 1, 2003 to December 31, 2015, a cohort of 1,208,710 women aged ≥30 years underwent cotesting (concurrent HPV and cytology screening). For each woman, we considered the first available cotest in this study period as “enrollment”. Cervical histopathology outcomes were collected for women through December 31, 2015. The KPNC institutional review board (IRB) approved use of the data, and National Institutes of Health Office of Human Subjects Research and Albert Einstein College of Medicine IRBs deemed this study exempt from review.

Screening and Clinical Management

Women were screened by HPV and cytology/cervical cytology testing as previously described [13]. Women were followed according to internal Kaiser guidelines, which were broadly concordant with national standards at the time [5, 14–16]. Women who cotested

HPV negative and cytology negative (Negative for Intraepithelial Lesion or Malignancy) (HPV−/cytology−), were offered screening again in 3 years. Women with cytologic abnormalities were referred to colposcopy per national recommendations [14, 16, 17]. The KPNC management of women with HPV-positive/cytology-negative (HPV+/cytology−) or HPV-negative/cytology-equivocal (HPV−/ASC-US) results evolved over time as previously described [12]. Observation with repeated colposcopy was elected for some younger women with cervical intraepithelial neoplasia grade 2 (CIN2), as nationally recommended [17, 18].

Statistical Analyses

We reviewed the case histories (computerized KPNC clinic and laboratory records) of the cancers included in this analysis to understand why cancer may have occurred. We assumed that any cancer diagnosed within a year of the first cotest, any regional or distant cancers diagnosed within two years of a first cotest, or any cancer diagnosed following a cytology result of cancer was already prevalent cancer at the time of or shortly after the first cotest. The natural history of HPV infection and cervical cancer is relatively slow, typically taking decades [19], which is why screening and treatment of precursor lesions has been successful in preventing cervical cancer. One model of the natural history of HPV infection and cervical cancer estimated that the median transition time from CIN2/3 to cervical cancer is 23.6 years and only 1.6% of CIN2/3 transition to cervical cancer in less than 10 years [20]. Invasive cervical cancer is extremely rare within 10 years of the population median age of sexual initiation [21], when exposure to HPV first occurs. Thus, it seems highly likely that most of the cancers classified by the above criteria would be either prevalent cancers or CIN3 on the verge of being invasive and virtually none resulting from an incident HPV infection or even incident CIN3.

We used contingency tables with Fisher's exact test for category variables to compare the last cotesting results prior to diagnosis, taking into account histology category, cancer stage, and prevalent versus incident cases. Kruskal-Wallis test was used to compare median values for age at diagnosis and time from last cotest to diagnosis between prevalent and incident cases. Logistic regression was used to calculate odds ratio (OR) with 95% confidence interval (95%CI) as a measure of association.

For incident cancers, we classified the programmatic correlates of cervical cancer diagnosis based on review of the clinical history. These categories were: A) *false-negative cotests/ sampling errors* (HPV−/cytology−) were defined as those that preceded a cancer diagnosis by one to four years; a negative cotest within one year of diagnosis was ignored (under the assumption that the cancer was already present) and the previous cotesting history was considered; B) *Algorithm delays* Algorithm delays were defined as women with localized cancers diagnosed 1–2 years following a cotest of HPV+/cytology− or HPV−/ASC-US without an intervening cotest (because 1-year follow-up and retesting was routinely recommended rather than immediate referral to colposcopy); C) *false-negative diagnoses* were those colposcopic evaluations one to five years prior to the cancer diagnosis that did not yield ≥CIN2 histopathology either due to the failure of colposcopy to biopsy the ≥CIN2 lesion or failure of pathology to diagnose it; D) *treatment failures* were those women treated for ≥CIN2 one to five years prior to the cancer diagnosis. Although treatments that occurred

more than 5 years prior to cancer diagnosis could also be categorized as treatment failures, we judged that more than 5 years was sufficient time to find, detect, and treat any residual precancerous lesion after the initial treatment; E) *non-compliance* indicated that women did not undergo follow-up (colposcopy or one-year retesting) or rescreening (3-year interval) within the time window of recommended time to the next visit plus a one-year grace period.

To put the occurrence of cancer into context of the cervical cancer screening program, we defined and calculated a surrogate measure of programmatic effectiveness, precancers/(precancers and cancers), assuming that detection cervical intraepithelial neoplasia grade 3 (CIN3) and adenocarcinoma *in situ* (AIS) (CIN3/AIS) was a screening success and cancers while were essentially failures to detect and treat CIN3/AIS prior to the development of invasive cervical cancer. For this analysis, we reasonably assumed (approximated) that all CIN3/AIS was successfully treated, given the efficacy of excisional treatments to treat CIN3/AIS [22]. We also calculated diagnostic yield, precancers per 1,000 cotests or precancers and cancers per 1,000 cotests, as surrogate measure of programmatic efficiency. These measures were calculated overall and stratified by age (30–39, 40–49, and 50 years and older). A trend with age was tested for statistical significance using a non-parametric test of trend [23]. We considered a higher percentage to represent greater effectiveness, while recognizing that many but not all precancers would invade if untreated [24]. At present, despite the inherent over-diagnosis, CIN3 or AIS represent our best current surrogate endpoint of cancer risk and screening target. Nor can we predict which CIN3 or AIS, if left untreated, will eventually become invasive. Although the typical treatment threshold is cervical intraepithelial neoplasia (CIN) grade 2 (CIN2), this threshold further emphasizes safety at the expense of over-treatment. Results were presented for all disease and separately for squamous disease (CIN3/SCC) and glandular disease (AIS/adenocarcinoma [ADC]). Cancers deemed prevalent were included or excluded in the cancer total in different “sensitivity” analyses.

Results

Using the medical records, 907 cervical cancers were identified. We excluded 55 cases (6.1%) diagnosed in women younger than 30 years because cotesting was not routinely performed in this age group, and 229 cases (25.2%) because they did not have a cotesting result prior to diagnosis, and thereby could not inform the questions that we were addressing. As result of these exclusions, there were 623 cervical cancers with at least one cotest up to the date of diagnosis (“pre-diagnostic” cotests) included in this analysis. Cancers were categorized as squamous cell carcinoma (SCC), ADC (including adenosquamous carcinoma), microinvasive cancer regardless of histology type, and cancers of other or uncertain histology (Other Cancers). Stage data was based on the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program classification (https://www.cancer.gov/about-cancer/diagnosis-staging/staging), there were 455 (73.0%) cancer cases with stage data, of which 333 (73.2%) were localized, 93 (20.4%) were regional, and 29 (6.4%) were distant.

Of the 623 cancers (68.7%) included in this analysis, there were 351 (56.3%) squamous cell carcinomas, 212 (34.0%) adenocarcinomas (including 19 adenosquamous carcinomas, 3

adenocarcinomas that favored endocervical [vs. endometrial] tissue, and 9 cases in which there was uncertainty as to whether the cancer tissue was endocervical or endometrial), 41 (6.6%) microinvasive cancers of unreported histology (classified as unknown histology), and 19 (3.0%) Other Cancers (listed in Supplemental Table 1). There was no difference in the distribution of diagnostic categories between cancers included in and excluded from these analyses (p=0.7).

Characteristics of the 623 women with cervical cancer included in these analyses are shown in Table 1, also stratified by whether the cancer was judged to be prevalent (i.e., already present at the time of the first cotest) (n=360, 57.8%) or incident (n=263, 42.2%). Prevalent cancers were more likely than incident cancers to be SCC (63.1% vs. 47.1%, respectively, p<0.001). Restricted to SCC and ADC, SCC was associated with prevalent cancers (OR=2.0, 95%CI=1.4–2.9).

Prevalent cancers were more likely than incident cancers to be HPV positive on the antecedent (last) cotest (89.2% vs. 80.2%, p=0.002). Prevalent cancers were more likely to have non-normal cytology (ASC-US or more severe) (91.1% vs. 70.7%, p<0.001), high-grade cytology (SCC, HSIL/AIS, ASC-H, or AGC) (78.9% vs. 54.0%, p<0.001), and, among those with high-grade cytology, more severe cytologic interpretations (SCC/Cancer > HSIL/AIS > AGC > ASC-H) (p_{trend}<0.001) (data not shown), than incident cancers on the antecedent cotest. There was no difference in the likelihood that the last (antecedent) cotest was cytology positive than HPV positive among prevalent cases (91.1% vs. 89.2%, respectively, p=0.3) whereas cytology was less likely to be positive (ASC-US or more severe) than HPV positive for an incident cancer (70.7% vs. 80.2%, respectively, p<0.001).

Only 44 (12.2%) of these prevalent cases had a cytology-only result prior to their first cotest in the KPNC database, 33 (75.0%) of which were (likely falsely) cytology negative. These prevalent cases (with respect to the first cotest) with preceding cytology did not differ in the SCC:ADC ratio from those without a preceding cytology (p=0.5) (data not shown). These prevalent cases (with respect to the first cotest) with preceding cytology were 13 years younger at diagnosis (34 years vs. 47 years, respectively, p<0.0001) and were more likely to be Caucasian or American Indian and less likely to be unreported or other race/ethnicity than those without a preceding cytology (p=0.007) (data not shown).

Among those 290 women with prevalent cancers at the time of their first cotest who had no history of cytology-only testing at KPNC during the study period prior to the cotest, did not have their first cotest at an age of 65 years and older, and appeared to have continuous coverage, we noted that there was a median and mean time of 891 and 2,023 days, respectively, between the date of last becoming a member their first cotest. Two-thirds of the women had a year or more time between the date of last becoming a member and their first cotest.

As a sensitivity analysis, using a definition of prevalent cancer as the first cotest two years prior to a localized cancer and three years prior to regional/distant cancer diagnoses, there were 430 prevalent cases and 193 incident cases (data not shown). Prevalent cancers were more likely than incident cancers to be SCC (60.2% vs. 47.7%, respectively, p=0.009).

Restricted to SCC and ADC, SCC was associated with prevalent cancers (OR=1.7, 95%CI=1.2–2.5).

We tabulated programmatic causes related to cancer diagnoses (Table 2). False-negative cotests/sampling errors (both HPV and cytology negative) were obtained prior to 11.2% of all cancers and 26.6% of incident cancers. False-negative diagnoses among women that screened positive (but were not diagnosed as CIN2 or more severe at colposcopy) were related to 9.0% of all cancers (21.3% of all incident cancers). Non-compliance with guidelines for screening and/or follow-up care were related to 9.0% of all cancers (21.3% of all incident cancers).

There was significant heterogeneity in the causes of cancer across histology categories ($p<0.001$). Prevalent cancer was much more common among SCC than ADC and Other Cancers. Restricted to incident cancers, significant heterogeneity remained ($p=0.002$). Notably, false-negative cotests/sampling errors was marginally associated with the cancer category ($p=0.07$) while algorithm delays and treatment failures were significantly associated with the cancer category ($p=0.04$ and $p<0.001$, respectively). False-negative cotests/sampling errors were particularly common (53.8%) among rare, incident Other Cancers; false-negative cotests/sampling errors preceded two clear cell carcinonomas, one small cell carcinonoma, one poorly differentiated adenocarcinoma carcinoma with a small cell component, two poorly differentiated cervical cancers, and one endocervical cancer with minimum deviation. Some of these cases may truly be unrelated to high-risk HPV (i.e., HPV-negative cervical cancer), as was observed in a recent report on the molecular characterization of cervical cancer [25], although it is of note that they were also cytology negative as well.

Notably, 13.7% of all ADC and 26.1% of incident ADC were attributed to algorithm delays. There was no statistically significant differences in the percentage of cancers due to non-compliance with guidelines across diagnostic categories. Presented in Supplemental Table 2 are instructive examples of false-negative screening, false-negative colposcopy, and treatment failure clinical histories prior to the cancer diagnoses.

Among those incident cases with stage data, there was significant heterogeneity in stage by causes of cancer ($p<0.001$). False-negative screening more strongly associated with regional/distant stage (vs. localized stage) compared to all other causes of cancer (42.0% vs. 16.0%, respectively, $p<0.001$; OR=3.8, 95%CI=1.7–8.5).

In Table 3, we compared that last cotesting results with histology and stage. HPV-positive cases were more likely to be unknown histology/microinvasive cancers while HPV-negative cases were more likely to be Other Cancers ($p<0.001$). HPV-positive cases were more likely to be localized cancers while HPV-negative cases were more likely to be regional cancers ($p<0.001$). Cytology-positive cancers were more likely to be SCC while cytology-negative cases were more likely to be ADC or Other Cancers ($p<0.001$). Cytology-positive cases were marginally more likely to be localized cancers while cytology-negative cases were more likely to be regional or distant cancers ($p=0.05$). HPV-positive, cytology-negative cases were associated with SCC (vs. ADC) (OR=3.5, 95%CI=1.34–9.0) and associated with

localized (vs. regional/distant cancers)(OR=5.3, 95%CI=1.6–19) compared to HPV-negative, cytology positive cases.

We used logistic regression to examine the independent association of last cotest results, histology, and race/ethnicity with prevalent (vs. incident) cancer (Table 4). Testing HPV positive was not associated with prevalent disease. Compared to those with an antecedent low-grade (LSIL or ASC-US) cytology, a negative cytology was negatively associated (OR=0.48, 95%=0.25–0.92) and high-grade cytology was positively associated (OR=1.9, 1.2–3.1) with a prevalent cancer (vs. incident). Compared to SCC, ADC was negative associated (OR=0.54, 95%CI=0.37–0.78) with prevalent cancer (vs. incident). Women who did not report their ethnicity were more likely to have prevalent cancer (vs. incident) (OR=7.9, 95%CI=2.2–28) compared to Caucasians or other racial/ethnic categories (e.g., African-American and other).

The programmatic effectiveness was 89.6%, and excluding prevalent cancers, 95.3% (Table 4). Considering microinvasive cancers as a screening success (i.e., precancer), this percentage was 90.3% and excluding prevalent cancers, 95.6%. The percentage was greater for squamous diseases (CIN3 vs. SCC) than for glandular diseases (AIS/ADC), overall (97.5% vs. 79.9%, respectively) and for each age group ($p<0.0001$ for all comparisons). The effectiveness decreased with increasing age ($p_{trend}<0.0001$). There was also decrease in the yield of precancers and cancers or precancers only per 1,000 cotests ($p_{trend}<0.0001$ for all comparisons) with older ages at first cotest.

Discussion

Here we report for the first time a systematic evaluation of cancers diagnosed within the first and most extensive HPV and cytology cotesting program in the U.S. Even in a state-of-art organized screening program that has deployed very sensitive triennial screening with cotesting and, as noted below, uses computerized patient tracking to increase compliance, cervical cancers still occurred albeit very rarely. Thus, we need to acknowledge that *no* real-world cervical cancer-screening program is likely to achieve perfect cervical cancer prevention.

The majority of cervical cancers were judged to be prevalent, i.e., cases that were diagnosed very soon after the first cotest; we were not evaluating the performance of the prior cytology-only screening program. The other, incident cancer diagnoses occurring subsequent to introduction of cotesting were slightly delayed in diagnosis following the guidelines mandating return testing for the common results of HPV+ cytology- or HPV− ASC-US (algorithmic delays).

Algorithmic delays (n=48 cases) were mostly commonly associated with ADC (29 or 60.4%); importantly, 31 of 32 (97%) cases of cancer with staging data that were attributed to algorithm delays were localized cancers. The first HPV+/cytology− result, a common antecedent cotest result to an ADC diagnosis, generally did not result in referral to colposcopy per KPNC and national guidelines [17]. Yet, sending all HPV-positive women to colposcopy is not advisable because the ratio of benign HPV infections to clinically relevant

HPV infections, those associated with precancer and specifically AIS, would be high resulting in lower overall health benefits-to-harms ratio. That is, current guidelines favor some degree of specificity over small incremental gains in sensitivity by not immediately referring HPV+/cytology− to colposcopy. Since approximately 15% of all incident cancers had an antecedent HPV+/cytology− result, better triage of HPV-positive results than cytology might further reduce the incidence of cancer by specifically referring women at higher risk for cancer to colposcopy. Potential strategies to improve sensitivity for identifying HPV-positive women with precancer or cancer include HPV genotyping [26–29], p16 immunocytochemistry [30–32], and informed or prejudicial review of cytology [33] as well as other biomarkers in the development pipeline [34].

KPNC has instituted a series of quality improvements to maximize programmatic performance. For example, the KPNC colposcopy guideline since 2008 is to perform four cervical microbiopsies and endocervical curettage at every colposcopy, which has been shown to increase the detection of ≥CIN2 [35]. Another example is that in 2005 a computerized tracking system was instituted that contains the updated follow-up protocols and intervals, examines the laboratory databases nightly, and tracks whether the recommended follow-up has been completed. In the absence of timely follow-up, there is an escalating series of alarms notifying staff, then providers, then the department chairperson and finally the facility Physician-In-Chief. Whether these changes have reduced the incidence of cervical cancer at KPNC is difficult to assess due to the year-to-year variability in the number of women diagnosed and treated for ≥CIN2 due partly to other changes in care and changes in membership over time.

The KPNC program was very effective, with 19 of 20 potentially precancerous lesions detected and presumably treated (Table 4) before some of them would go on to become invasive cancer. If screening and management are more effective for the prevention of SCC than ADC, then the ratio of the two (SCC:ADC) becomes a marker for the impact of screening, with effective screening resulting in a lower SCC:ADC. To that point, SCC:ADC (1.7:1.0) was much lower at KPNC than observed in SEER (2.5:1.0) during this same time period [36], suggesting the KPNC program is significantly more effective than average screening program in the U.S. The SCC:ADC was considerably higher for cancers deemed as prevalent (2.2:1) than those that were considered incident (1.1:1).

Therefore, there appears to be some validity to our definition of prevalent cases, which constituted the majority of cervical cancers diagnosed in women undergoing cotesting at KPNC. We suggest that many of these women with prevalent cancer may have become new members at KPNC within the 1–2 years prior to diagnosis and, as inferred from the SCC:ADC, were previously less well screened than those who were already in the KPNC system. The implication of these data is that some of the cervical cancers might be down-staged or even averted by encouraging earlier cotesting of women aged 30 years and older who join KPNC. Most women were went more than a year before their first cotesting.

One of the controversies in cervical screening is at what age to stop screening following a negative screening history [37–41]. Current guidelines [42] recommend that “Women aged older than 65 years with evidence of adequate negative prior screening and no history of

CIN2+ within the last 20 years should not be screened for cervicalcancer with any modality (adequate negative prior screening is defined as 3 consecutive negative cytology results or 2 consecutive negative cotests within the 10 years before ceasing screening, with the most recent test occurring within the past 5 years)". In our case series, five women aged 65 and older who were diagnosed with cancer had a history of two consecutive negative cotests (n.b., another 6 had a single negative cotest prior to diagnosis). However, the question of whether women aged 65 and older with a 10-year negative screening history that includes two negative cotests should be exited from routine screening is best determined by their absolute risk of cancer [43]. The question cannot be answered without knowing the denominator i.e., how many women met those exit criteria and did not get cancer? That is the subject of a future analysis using KPNC data. The other issue is that screening might not be effective in finding disease in these women, given that it was already missed twice by cotesting prior to exiting.

Another controversy is whether to screen with HPV testing alone or cotesting. The results for the last cotest prior to diagnosis (Table 3) must be interpreted with caution as these cases represent a bias set of cancers that were likely missed by previous cervical screens. Thus, the sensitivity of HPV vs. cotesting for any case of invasive cervical cancer cannot be extrapolated directly from these data. Indeed, when split into prevalent and incident cancers (Table 1), prevalent cases were more likely to test HPV and cytology positive than the incident cases.

There were clear limitations of this analysis. First, as with any retrospective review of cases, our ability to attribute cancer cases to specific programmatic causes was limited by the data available to us, which were incomplete. This is especially true for women coming into the KPNC program from another screening program. Second, we did we know the specifics of why certain tests or procedures were done at any given time. Third, we did not know when the cancer actually developed versus when it was diagnosed. Fourth, we had no way to determine whether non-compliance with KPNC guidelines was at the patient, provider, or system level. Finally, our definitions of the causes of cancer, while rational, were arbitrary because we do not know actually why cancer occurred. In our sensitivity analysis, the two-year interval between the first cotest and localized cancer and three-year interval between the first cotest and regional/distant cancer, significantly increased the number of cancers classified as prevalent but somewhat lowered the SCC:ADC ratio. Choosing a 6-month window of time to define cancers that were prevalent at the time of the first cotest, irrespective of stage, only excluded ~11% of the cases as prevalent. Our choice of the one-year interval between the first cotest and localized cancer and two-year interval between the first cotest and regional/distant cancer was likely more specific but not as sensitive a definition of prevalent cancer as the one used in the sensitivity analysis.

The introduction of HPV testing into routine cervical cancer screening has led to reasonably safe interval extension between screens [44]. Nevertheless, due to a variety of reasons, cervical cancer continues to occur, albeit rarely, even in a well-organized, state-of-the-art cervical cancer-screening program such as KPNC. Whether better medical record tracking for women switching from one health plan to another and/or aggressively targeted screening

of new members upon entry into any health plan could avert some additional cancers may warrant further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Castle received partial support by the Intergovernmental Personnel Act mobility program with the NCI.

Reference List

1. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet. 2007; 370:890–907. [PubMed: 17826171]
2. Ronco G, Dillner J, Elfstrom KM, Tunesi S, Snijders PJ, Arbyn M, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 2014; 383:524–32. [PubMed: 24192252]
3. Cuzick J, Clavel C, Petry KU, Meijer CJ, Hoyer H, Ratnam S, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. Int J Cancer. 2006; 119:1095–101. [PubMed: 16586444]
4. Castle PE, de SS, Qiao YL, Belinson JL, Lazcano-Ponce E, Kinney W. Introduction of human papillomavirus DNA screening in the world: 15 years of experience. Vaccine. 2012; 30(Suppl 5):F117–F122. [PubMed: 23199954]
5. Wright TC Jr, Schiffman M, Solomon D, Cox JT, Garcia F, Goldie S, et al. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. Obstet Gynecol. 2004; 103:304–9. [PubMed: 14754700]
6. Kinney W, Wright TC, Dinkelspiel HE, DeFrancesco M, Thomas CJ, Huh W. Increased cervical cancer risk associated with screening at longer intervals. Obstet Gynecol. 2015; 125:311–5. [PubMed: 25568989]
7. Felix JC, Lacey MJ, Miller JD, Lenhart GM, Spitzer M, Kulkarni R. The Clinical and Economic Benefits of Co-Testing Versus Primary HPV Testing for Cervical Cancer Screening: A Modeling Analysis. J Womens Health (Larchmt). 2016
8. Naber SK, De Kok IM, Matthijsse SM, van BM. The potential harms of primary human papillomavirus screening in over-screened women: a microsimulation study. Cancer Causes Control. 2016; 27:569–81. [PubMed: 26970740]
9. Davis M, Feldman S. Making Sense of Cervical Cancer Screening Guidelines and Recommendations. Curr Treat Options Oncol. 2015; 16:55–0373. [PubMed: 26467929]
10. Wentzensen N, Arbyn M. HPV-based cervical cancer screening-facts, fiction, and misperceptions. Prev Med. 2017; 98:33–35. 33–5. Epub;%2017 Feb 6. DOI: 10.1016/j.ypmed.2016.12.040 [PubMed: 28279260]
11. May 28. 2015 http://www.uspreventiveservicestaskforce.org/Page/Document/draft-research-plan179/cervical-cancer-screening2Ref Type: Internet Communication
12. Katki HA, Kinney WK, Fetterman B, Lorey T, Poitras NE, Cheung L, et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. Lancet Oncol. 2011; 12:663–72. [PubMed: 21684207]
13. Gage JC, Schiffman M, Katki HA, Castle PE, Fetterman B, Wentzensen N, et al. Reassurance against future risk of precancer and cancer conferred by a negative human papillomavirus test. J Natl Cancer Inst. 2014; 106:dju153. [PubMed: 25038467]
14. Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA. 2002; 287:2120–9. [PubMed: 11966387]

15. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. J Low Genit Tract Dis. 2007; 11:223–39. [PubMed: 17917567]
16. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with abnormal cervical screening tests. J Low Genit Tract Dis. 2007; 11:201–22. [PubMed: 17917566]
17. Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 2013; 17:S1–S27. [PubMed: 23519301]
18. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. Am J Obstet Gynecol. 2007; 197:340–5. [PubMed: 17904956]
19. Moscicki AB, Schiffman M, Burchell A, Albero G, Giuliano AR, Goodman MT, et al. Updating the natural history of human papillomavirus and anogenital cancers. Vaccine. 2012; 30(Suppl 5):F24–33. %20. DOI: 10.1016/j.vaccine.2012.05.089 [PubMed: 23199964]
20. Vink MA, Bogaards JA, van Kemenade FJ, de Melker HE, Meijer CJ, Berkhof J. Clinical progression of high-grade cervical intraepithelial neoplasia: estimating the time to preclinical cervical cancer from doubly censored national registry data. Am J Epidemiol. 2013; 178:1161–9. [PubMed: 23897645]
21. Plummer M, Peto J, Franceschi S. Time since first sexual intercourse and the risk of cervical cancer. Int J Cancer. 2012; 130:2638–44. [PubMed: 21702036]
22. Santesso N, Mustafa RA, Wiercioch W, Kehar R, Gandhi S, Chen Y, et al. Systematic reviews and meta-analyses of benefits and harms of cryotherapy, LEEP, and cold knife conization to treat cervical intraepithelial neoplasia. Int J Gynaecol Obstet. 2016; 132:266–71. [PubMed: 26643302]
23. Cuzick J. A Wilcoxon-type test for trend. Stat Med. 1985; 4:87–90. [PubMed: 3992076]
24. McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol. 2008; 9:425–34. [PubMed: 18407790]
25. Integrated genomic and molecular characterization of cervical cancer. Nature. 2017; 543:378–84. [PubMed: 28112728]
26. Khan MJ, Castle PE, Lorincz AT, Wacholder S, Sherman M, Scott DR, et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. J Natl Cancer Inst. 2005; 97:1072–9. [PubMed: 16030305]
27. Castle PE, Solomon D, Schiffman M, Wheeler CM. Human papillomavirus type 16 infections and 2-year absolute risk of cervical precancer in women with equivocal or mild cytologic abnormalities. J Natl Cancer Inst. 2005; 97:1066–71. [PubMed: 16030304]
28. Castle PE, Glass AG, Rush BB, Scott DR, Wentzensen N, Gage JC, et al. Clinical human papillomavirus detection forecasts cervical cancer risk in women over 18 years of follow-up. J Clin Oncol. 2012; 30:3044–50. [PubMed: 22851570]
29. Castle PE, Stoler MH, Wright TC Jr, Sharma A, Wright TL, Behrens CM. Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study. Lancet Oncol. 2011; 12:880–90. [PubMed: 21865084]
30. Carozzi F, Confortini M, Palma PD, Del MA, Gillio-Tos A, De ML, et al. Use of p16-INK4A overexpression to increase the specificity of human papillomavirus testing: a nested substudy of the NTCC randomised controlled trial. Lancet Oncol. 2008
31. Carozzi F, Gillio-Tos A, Confortini M, Del MA, Sani C, De ML, et al. Risk of high-grade cervical intraepithelial neoplasia during follow-up in HPV-positive women according to baseline p16-INK4A results: a prospective analysis of a nested substudy of the NTCC randomised controlled trial. Lancet Oncol. 2013; 14:168–76. [PubMed: 23261355]
32. Wentzensen N, Fetterman B, Castle PE, Schiffman M, Wood SN, Stiemerling E, et al. p16/Ki-67 Dual Stain Cytology for Detection of Cervical Precancer in HPV-Positive Women. J Natl Cancer Inst. 2015; 107:djv257. [PubMed: 26376685]

33. Bergeron C, Giorgi-Rossi P, Cas F, Schiboni ML, Ghiringhello B, Dalla PP, et al. Informed cytology for triaging HPV-positive women: substudy nested in the NTCC randomized controlled trial. J Natl Cancer Inst. 2015; 107:dju423. [PubMed: 25568167]
34. Sahasrabuddhe VV, Luhn P, Wentzensen N. Human papillomavirus and cervical cancer: biomarkers for improved prevention efforts. Future Microbiol. 2011; 6:1083–98. [PubMed: 21958146]
35. Pretorius RG, Zhang WH, Belinson JL, Huang MN, Wu LY, Zhang X, et al. Colposcopically directed biopsy, random cervical biopsy, and endocervical curettage in the diagnosis of cervical intraepithelial neoplasia II or worse. Am J Obstet Gynecol. 2004; 191:430–4. [PubMed: 15343217]
36. Surveillance, Epidemiology, and End Results (SEER) Program. U.S. National Cancer Institute; 2014. (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2013 Sub (1973–2011) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969–2012 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014, based on the November 2013 submission11-13-2014
37. Castanon A, Landy R, Cuzick J, Sasieni P. Cervical screening at age 50–64 years and the risk of cervical cancer at age 65 years and older: population-based case control study. PLoS Med. 2014; 11:e1001585. [PubMed: 24453946]
38. Sawaya GF, Kulasingam S, Denberg TD, Qaseem A. Cervical Cancer Screening in Average-Risk Women: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med. 2015; 162:851–9. [PubMed: 25928075]
39. Peirson L, Fitzpatrick-Lewis D, Ciliska D, Warren R. Screening for cervical cancer: a systematic review and meta-analysis. Syst Rev. 2013; 2:35. 35–2. [PubMed: 23706117]
40. White MC, Shoemaker ML, Benard VB. Cervical Cancer Screening and Incidence by Age: Unmet Needs Near and After the Stopping Age for Screening. Am J Prev Med. 2017; 10
41. Rositch AF, Nowak RG, Gravitt PE. Increased age and race-specific incidence of cervical cancer after correction for hysterectomy prevalence in the United States from 2000 to 2009. Cancer. 2014; 120:2032–8. [PubMed: 24821088]
42. Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin. 2012; 62:147–72. [PubMed: 22422631]
43. Castle PE, Sideri M, Jeronimo J, Solomon D, Schiffman M. Risk assessment to guide the prevention of cervical cancer. J Low Genit Tract Dis. 2008; 12:1–7. [PubMed: 18162804]
44. Silver MI, Schiffman M, Fetterman B, Poitras NE, Gage JC, Wentzensen N, et al. The population impact of human papillomavirus/cytology cervical cotesting at 3-year intervals: Reduced cervical cancer risk and decreased yield of precancer per screen. Cancer. 2016; 10

Table 1

A comparison of cancers classified as prevalent versus those not prevalent. Abbreviations: SCC, squamous cell carcinoma; ADC, adenocarcinoma; HPV, human papillomavirus; HPV+, HPV positive; HPV−, HPV negative; Cyto+, cytology positive (ASC-US or more severe); Cyto−, cytology negative (normal); AGC, atypical glandular cells; HSIL, high-grade squamous intraepithelial lesion; AIS, adenocarcinoma *in situ*; ASC-H, atypical squamous cells cannot rule out HSIL; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion

	Total (n = 623)		**Prevalent (n = 360)**		**Incident (n = 263)**		
	n	**%col**	**n**	**%col**	**n**	**%col**	**p**
Histology							
SCC	351	56.3%	227	63.1%	124	47.1%	<0.001
ADC	212	34.0%	101	28.1%	111	42.2%	
Other	19	3.0%	6	1.7%	13	4.9%	
Unknown[≠]	41	6.6%	26	7.2%	15	5.7%	
Stage							
Localized	333	53.5%	199	55.3%	134	51.0%	0.02
Regional (all)	93	14.9%	64	17.8%	29	11.0%	
Lymph Nodes	28	4.5%	16	4.4%	12	4.6%	
Extension	46	7.4%	34	9.4%	12	4.6%	
Lymp Nodes&Extension	19	3.0%	14	3.9%	5	1.9%	
Distant	29	4.7%	17	4.7%	12	4.6%	
Unknown	4	0.6%	2	0.6%	2	0.8%	
Missing	164	26.3%	78	21.7%	86	32.7%	
Last Cotest Prior to Diagnosis							
HPV+	532	85.4%	321	89.2%	211	80.2%	0.002
Cyto+	514	82.5%	328	91.1%	186	70.7%	<0.001
HPV−/Cyto−	51	8.2%	12	3.3%	39	14.8%	<0.001
HPV−/Cyto+	40	6.4%	27	7.5%	13	4.9%	
HPV+/Cyto−	58	9.3%	20	5.6%	38	14.4%	
HPV+/Cyto+	474	76.1%	301	83.6%	173	65.8%	

	Total (n = 623)		Prevalent (n = 360)		Incident (n = 263)		
	n	%col	n	%col	n	%col	p
Negative/NILM *	109	17.5%	32	8.9%	77	29.3%	<0.001
AGC	91	14.6%	45	12.5%	46	17.5%	
ASC-H	64	10.3%	31	8.6%	33	12.5%	
ASC-US	65	10.4%	30	8.3%	35	13.3%	
HSIL/AIS	210	33.7%	154	42.8%	56	21.3%	
LSIL/CIN1	23	3.7%	14	3.9%	9	3.4%	
SCC	59	9.5%	52	14.4%	7	2.7%	
Other Malignancy	2	0.3%	2	0.6%	0	0.0%	
High-Grade Cytology **	426	68.4%	284	78.9%	142	54.0%	<0.001
Race/Ethnicity							
African-American	42	6.7%	22	6.1%	20	7.6%	0.02
Native American	5	0.8%	2	0.6%	3	1.1%	
Asian	83	13.3%	52	14.4%	31	11.8%	
Caucasian	346	55.5%	192	53.3%	154	58.6%	
Hispanic	104	16.7%	58	16.1%	46	17.5%	
Other	15	2.4%	9	2.5%	6	2.3%	
Unreported	28	4.5%	25	6.9%	3	1.1%	
	Median/Mean/Range		Median/Mean/Range		Median/Mean/Range		P
Number of Cotests	1/1.85/1–11		1/1/1–3		2/2.88/1–11		<0.001
Age at First Cotest (Years)	43/46/30–67		47/47/30–66		42/45/30–67		0.03
Age at Cancer Diagnosis (Years)	47/48/30–75		46/47/30–68		47/49/31–75		0.08
Time From First Cotest to Diagnosis (Years)	0.41/1.87/12.0-0		0.14/0.23/1.93-0		3.48/4.12/12.0-1.01		<0.001
Time From Last Cotest to Diagnosis (Years)	0.17/0.32/10.9-0		0.12/0.18/1.85-0		0.24/0.70/10.9-0		<0.001

* AGC, ASC-H, HSIL/AIS, SCC, or other malignancy cytology

** Includes unsatisfactory cytology, 3 for prevalent and 3 for not prevalent

≠ The histology of microinvasive cancers was not available

Table 2

A evaluation of the programmatic correlates leading to cervical cancer diagnoses. Abbreviations: SCC, squamous cell carcinoma, ADC, adenocarcinoma

Programmatic Correlates of Cervical Cancer Diagnoses	All n=623			SCC n=351			ADC n=212			Other Cancers n=19			Unknown‡ n=41			
	n	% col	% col′	n	% col	% col′	n	% col	% col′	n	% col	% col′	n	% col	% col′	p*
Prevalent Cancers	360	57.8%	---	227	64.7%	---	101	47.6%	---	6	31.6%	---	26	63.4%	---	<0.001
Non-Prevalent Cancers	263	42.2%	100%	124	35.3%	100%	111	52.4%	100%	13	68.4%	100%	15	36.6%	100%	<0.001
False-Negative Cotest (Screen)	70	11.2%	26.6%	36	10.3%	29.0%	25	11.8%	22.5%	7	36.8%	53.8%	2	4.9%	13.3%	0.07
Algorithm Delays	48	7.7%	18.3%	15	4.3%	12.1%	29	13.7%	26.1%	2	10.5%	15.4%	2	4.9%	13.3%	0.04
False-Negative Diagnoses (Colposcopy and Biopsy)	56	9.0%	21.3%	20	5.7%	16.1%	28	13.2%	25.2%	3	15.8%	23.1%	5	12.2%	33.3%	0.2
Treatment Failure	27	4.3%	10.3%	23	6.6%	18.5%	3	1.4%	2.7%	0	0.0%	0.0%	1	2.4%	6.7%	<0.001
Non-Compliance with Guidelines (All)	56	9.0%	21.3%	29	8.3%	23.4%	21	9.9%	18.9%	1	5.3%	7.7%	5	12.2%	33.3%	0.9
Non-Complaince with Screening	9	1.4%	3.4%	4	1.1%	3.2%	4	1.9%	3.6%	1	5.3%	7.7%	0	0.0%	0.0%	0.6
Non-Compliance with Follow-Up†	45	7.2%	17.1%	23	6.6%	18.5%	17	8.0%	15.3%	0	0.0%	0.0%	5	12.2%	33.3%	0.1
Non-Compliance with Screening and Follow-Up	2	0.3%	0.8%	2	0.6%	1.6%	0	0.0%	0.0%	0	0.0%	0.0%	0	0.0%	0.0%	0.6
Mixed**	6	1.0%	2.3%	1	0.3%	0.8%	5	2.4%	4.5%	0	0.0%	0.0%	0	0.0%	0.0%	0.3

** Several possible explanations

‘column percentage among non-prevalent cancers

* Fisher’s exact test for differences for a correlate by histology category among non-prevalent cancers

‡ The histology of microinvasive cancers was not available

† Includes failure to come back for follow-up testing, colposcopy, treatment, or post-treatment surveillance according to recommendations

Table 3

The relationship of last cotesting results with histology and cancer stage. Abbreviations: SCC, squamous cell carcinoma; ADC, adenocarcinoma; HPV, human papillomavirus; Cyto, cytology

	HPV+ (n=532)		HPV− (n=91)		Cyto+ (n=514)		Cyto- (n=108)		HPV−/Cyto− (n=51)		HPV−/Cyto+ (n=40)		HPV+/Cyto− (n=58)		HPV+/Cyto+ (n=474)	
	n	%col	n	%col	n	%col	n	%col	n	%col	n	%col	n	%col	n	%col
Histology																
SCC	298	56.0%	53	58.2%	309	60.1%	42	38.9%	27	52.9%	26	65.0%	15	25.9%	283	59.7%
ADC	185	34.8%	27	29.7%	158	30.7%	54	50.0%	17	33.3%	10	25.0%	37	63.8%	148	31.2%
Other	9	1.7%	10	11.0%	8	1.6%	11	10.2%	7	13.7%	3	7.5%	4	6.9%	5	1.1%
Unknown‡	40	7.5%	1	1.1%	39	7.6%	2	1.9%	0	0.0%	1	2.5%	2	3.5%	38	8.0%
Stage																
Localized	302	56.8%	31	34.1%	285	55.4%	48	44.4%	14	27.5%	17	42.5%	34	58.6%	268	56.5%
Regional (all)	67	12.6%	26	28.6%	72	14.0%	21	19.4%	15	29.4%	11	27.5%	6	10.3%	61	12.9%
Distant	15	2.8%	14	15.4%	20	3.9%	9	8.3%	9	17.7%	5	12.5%	0	0.0%	15	3.2%
Unknown/Missing	148	27.8%	20	22.0%	137	26.7%	31	28.7%	13	25.5%	7	17.5%	18	31.0%	130	27.4%

Table 4

A logistic regression model to determine the odds ratio (OR) and 95% confidence interval (95%CI) as a measure of association with whether the cancer was categorized as prevalent (vs. not prevalent), last cytology and human papillomavirus (HPV) test results before cancer diagnosis, and histologic diagnosis category. Abbreviations: SCC, squamous cell carcinoma; ADC, adenocarcinoma

Cofactor	N	%	OR	95%CI
Last HPV result before diagnosis				
negative (ref)	91	14.6%	1.0	---
positive	532	85.4%	1.3	0.73–2.2
Last cytology result before diagnosis				
negative	109	17.5%	**0.48**	**0.25–0.92**
Low grade (ref)	88	14.1%	1.0	---
High grade	426	68.4%	**1.9**	**1.2–3.1**
Diagnosis				
SCC (ref)	351	56.3%	1.0	---
ADC	212	34.0%	**0.54**	**0.37–0.78**
Microinvasive	41	6.6%	0.79	0.39–1.6
Other	19	3.1%	0.49	0.17–1.4
Race				
Unknown	28	4.5%	**7.9**	**2.2–28**
Caucasian (ref)	346	55.5%	1.0	---
African American	42	6.7%	0.99	0.49–2.0
Other	207	33.2%	1.0	0.72–1.5

Table 5

The percentage of precancers to precancers and cancers and the percentage of precancers or precancers and cancers per 1,000 cotests. Analyses treated microinvasive cancer as screening failure (cancer) or success (precancer) and included or excluded those cancers deemed prevalent. Results were presented for all histologic types, for squamous and glandular disease separately. Results were also stratified by age at the time of their first cotest, categorized as 30–39, 40–49, and 50–77 years.

	All Women 2,754,229 Cotests				Women Aged 30–39 Years 1,114,462 Cotests				Women Aged 40–49 Years 815,430 Cotests				Women Aged 50–77 Years 824,337 Cotests			
	All*	All*†	Squamous	Glandular	All*	All*†	Squamous	Glandular	All*	All*†	Squamous	Glandular	All*	All*†	Squamous	Glandular
Number of Cervical Cancers	623	582	351	212	216	193	117	72	184	177	101	73	223	212	133	67
Number of Precancers (CIN3 or AIS)	5,369	5,410	4,929	440	3,371	3,394	3,079	292	1,212	1,219	1,113	99	786	797	737	49
Number of Precancers and Cervical Cancers	5,992	5,992	5,280	652	3,587	3,587	3,196	364	1,396	1,396	1,214	172	1,009	1,009	870	116
Percentage, Precancer/ (Precancer and Cancer)	89.6%	90.3%	93.4%	67.5%	94.0%	94.6%	96.3%	80.2%	86.8%	87.3%	91.7%	57.6%	77.9%	79.0%	84.7%	42.2%
Percentage, Precancer/ (Precancer and Cancer)≠	95.3%	95.6%	97.5%	79.9%	97.1%	97.4%	98.5%	88.0%	93.7%	93.8%	96.8%	70.7%	90.7%	91.0%	94.7%	62.0%
CIN3 or AIS per 1,000 Cotests	1.95	1.96	1.79	0.16	3.02	3.05	2.76	0.26	1.49	1.49	1.36	0.12	0.95	0.97	0.89	0.06
CIN3, AIS, or Cervical Cancer per 1,000 Cotests	2.18	2.18	1.92	0.24	3.22	3.22	2.87	0.33	1.71	1.71	1.49	0.21	1.22	1.22	1.06	0.14

*Includes Other Cancers

† Counting microinvasive cancers as precancers (including those classified as prevalent)

‡ Excluding prevalent cancers