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Contributions of Liquid-Based (Papanicolaou) Cytology and Human Papillomavirus Testing in Cotesting for Detection of Cervical Cancer and Precancer in the United States

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ABSTRACT

Objectives: *Given the recent debate challenging the contribution of cytology in cervical screening, we evaluated results of liquid-based cytology (LBC) and human papillomavirus (HPV) testing in cotesting preceding cervical cancer (CxCa) and precancer diagnoses in a national, heterogeneous population.*

Methods: *We assessed the results of cotesting, performed by Quest Diagnostics, in 13,633,071 women 30 years and older, tested 2010 to 2018. Cotest results preceding CxCa or precancer diagnoses were analyzed and stratified by histopathology.*

Results: *Among all screening results, 1,615 cotests preceded 1,259 CxCa diagnoses, and 11,164 cotests preceded 8,048 cervical precancer diagnoses. More women who were subsequently diagnosed with CxCa within 1 year were identified by the LBC result than by the HPV result (85.1%, 1,015/1,193 vs 77.5%, 925/1,193). Among all women with CxCa, the overall rate of nondetection was 13.1% (212/1,615) for cotesting results (LBC negative/HPV negative) and this rate increased substantially when testing exceeded 12 months compared to within 1 year prediagnosis of either CxCa or precancer.*

Conclusions: *Analysis of 9-year cotest results from a national reference laboratory confirms the value of LBC element in cotesting. This supports that LBC/HPV cotesting enhances screening for the identification of CxCa in women 30 years and older, more so than LBC or HPV alone within cotesting.*

Key Points

- Liquid-based cytology (LBC)/human papillomavirus (HPV) cotesting enhances screening for detection of cervical cancer in women 30 years and older, more so than LBC or HPV alone among women receiving cotesting.
- More women subsequently diagnosed with cervical cancer within 1 year of cotesting were identified by LBC than by the HPV (85.1%, 1,015/1,193 vs 77.5%, 925/1,193).
- Among women with cervical cancer, the false-negative rate was 13.1% (212/1,615) for cotesting results (LBC negative/HPV negative), and this rate increased substantially when testing was longer than 12 months.

Routine cervical screening of women 30 years and older using Papanicolaou (Pap) cytology and human papillomavirus (HPV) together (cotesting) was first approved by the US Food and Drug Administration (FDA) in 2003.[1] Since then, cotesting has steadily increased in the United States.[2] FDA-approved cotesting is the preferred method for cervical screening of women 30 years and older in current American College of Obstetricians and Gynecologists[3] guidelines and in joint guidelines from the American Cancer Society, American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology.[4]

More recently, however, the contribution of cytology to screening outcomes achievable with cytology and HPV cotesting has been questioned. This challenge to cotesting has been largely based on an analysis of data from Kaiser Permanente Northern California (KPNC), a relatively select geographic population with limited socioeconomic diversity.[5-9] The KNPC analysis used by the ASCCP to create new "risk-based management consensus guidelines"[10] evaluated 1,208,710 women 30 years and older

undergoing triennial cervical cotesting from 2003 until 2015. In addition to health plan members' easier access to care and more rigorous follow-up system, KPNC follows several unique cervical screening practices that are unusual in the United States. These practices include the exclusive use of the conventional Pap smear until 2009 coupled with the separate collection of cytology and HPV specimens.[5,9]

In another study from a large academic medical center, a comparative analysis of cotesting data using FDA-approved imaged liquid-based cytology (LBC) and from-the-vial HPV cotesting found that imaged LBC cotesting detected cervical cancer (CxCa) and precancer (cervical intraepithelial neoplasia grade 3 [CIN 3]/adenocarcinoma in situ [AIS]) more effectively than reported by KPNC.[11]

The current study retrospectively evaluated cervical cancer screening results from women 30 years and older who received cotesting from 2010 to 2018 at a national reference laboratory with a large, geographically and socioeconomically diverse population. Our goal was to determine the relative contributions of LBC and HPV tests within cotesting to the detection of CxCa and precancer.

Materials and Methods

From 2010 through 2018, there were 13,633,071 women 30 years and older with 18,832,014 cotest results in the Quest Diagnostics database. This study only included cervical cancer screening data from those women who had at least one LBC and HPV cotest prior to histopathologic diagnoses of CxCa or CIN 3/AIS. This database reflects a highly diverse, heterogeneous population across the United States, including approximately half of the adult population in the past 3 years. We analyzed cotesting data preceding CxCa and CIN 3/AIS diagnoses; some women had more than one cotest prior to a diagnosis.

LBC tests included both ThinPrep (Hologic)[12] and SurePath (Becton Dickinson)[13] Pap tests, many of which also employed computer-assisted ThinPrep or SurePath (BD FocalPoint) Imaging Systems.[14,15] Positive LBC results were defined as all results with epithelial cell abnormalities at or above the level of atypical squamous cells of underdetermined significance (ASC-US) using the Bethesda System.[16] From-the-vial high-risk HPV testing included the Digene Hybrid Capture 2 HPV test (DNA) (Qiagen)[17] and the Aptima HPV test (messenger RNA) (Hologic/Gen-Probe).[18] Cervical histopathology outcomes identified over the same study period included diagnoses of CxCa (squamous cell carcinoma [SCC], adenocarcinoma or adenosquamous carcinoma [ADC],

and other CxCa [other]) and cervical precancers or CIN 3/AIS.

To facilitate comparison, the results of this study are presented in an equivalent format to those published in two recent large studies.[5,11] McNemar χ^2 test was used to compare LBC and HPV tests, adjusting for within-subject effects. The distribution of cotest results prior to histopathologic CxCa or CIN 3/AIS diagnoses was plotted over time, including overall CxCa diagnoses, stratified by tumor histopathology (SCC, ADC), CIN 3/AIS, CIN 3 only, and AIS only. Prediagnosis cotest results were classified into four mutually exclusive categories: HPV positive/LBC positive, HPV positive/LBC negative, HPV negative/LBC positive, or HPV negative/LBC negative. The interval between cotest result and diagnosis was grouped into eight nonoverlapping time periods: less than 6 months, 6 months to less than 12 months, 1 year (12 months to <24 months), 2 years (24 months to <36 months), 3 years (36 months to <48 months), 4 years (48 months to <60 months), 5 years (60 months to <72 months), and 6 years or more (≥72 months). Data analyses were performed using SAS Studio 3.6 on SAS 9.4 (SAS Institute). This Quest Diagnostics Health Trends study was deemed exempt by the Western Institutional Review Board (Puyallup, WA).

Results

Cotesting Preceding Cervical Cancer Diagnoses

Among all screening results, 1,615 cotests preceding 1,259 cervical cancer diagnoses met study selection criteria ❚Table 1❚. Of the 1,615 cotests, 58% were SCC diagnoses, 30% were ADC diagnoses, and 12% were other CxCa diagnoses.

Of 1,615 cotest results prior to CxCa diagnoses, 73.6% (1,189/1,615) were LBC positive (ASC-US or more abnormal) and 71.6% (1,157/1,615) were HPV positive (P =.15); the difference in percentages of LBC positive and HPV positive was only statistically significant in other CxCa diagnoses (66% vs 46.7%, P < .0001), not in SCC or ADC diagnoses. Of all cotest results, 86.9% (1,403/1,615) were positive by either LBC testing or HPV or both. LBC-positive cotest results were more likely before SCC (82.3%, 773/939) than before ADC (59.7%, 286/479) or before other CxCa (66.0%, 130/197) (P < .001, not reported in table).

Cotesting Preceding Cervical Precancer Diagnoses

Among all screening results, 11,164 cotests preceding 8,048 cervical precancer diagnoses met study selection

criteria ❚Table 2❚. Of these 11,164 cotest results, 95.4% were for CIN 3 and 4.6% for AIS.

Of 11,164 cotest results preceding CIN 3/AIS diagnoses, 77.9% (8,697/11,164) were LBC positive and 92.6% (10,343/11,164) were HPV positive ($P < .0001$); HPV positive was more likely than LBC positive prior to CIN 3 (92.8%, 9,882/10,648 vs 78.8%, 8,395/10,648, $P < .0001$) or AIS (89.3%, 461/516 vs 58.5%, 302/516, $P < .0001$), respectively. Of all cotest results, 95.6% (10,671/11,164) were positive by either LBC testing or HPV or both.

Cotesting (<12 Months vs ≥12 Months) Prior to Diagnoses

When comparing cotest results performed less than 12 months to those performed 12 or more months preceding diagnoses, more positive (LBC positive and/or HPV positive) cotests occurred within 12 months of diagnosis for both CxCa and CIN 3/AIS diagnoses ❚Table 3❚. In testing within 12 months of diagnosis, LBC was more likely than HPV to be positive prior to CxCa diagnoses (85.1%, 1,051/1,193 vs 77.5%, 925/1,193, $P < .0001$), while HPV was more frequently positive than LBC prior to CIN 3/AIS diagnoses (97.6%, 7,827/8,022 vs 89.3%, 7,165/8,022, $P < .0001$). When the cotesting to diagnosis interval exceeded 12 months, HPV-positive results were more likely than LBC-positive results before both CxCa (55.0%, 232/422 vs 41.2%, 174/422, $P < .0001$) and CIN 3/AIS diagnoses (80.1%, 2,516/3,142 vs 48.8%, 1,532/3,142, $P < .0001$).

Cotesting Prior to Diagnoses by Time Period

Results of cotesting for various time periods prior to histopathology diagnoses are shown graphically in ❚Figure 1❚. The rates of positive cervical screening test results, LBC positive or HPV positive, declined as the interval between cotesting and CxCa or precancer diagnosis increased.

Discussion

This study evaluated the contributions of LBC and HPV in cervical cancer screening cotesting and reported a higher detection rate in LBC-positive cotest results than in HPV-positive cotest results in diagnosing CxCa within 1 year after cotesting. The findings were based on the largest and most diverse US cervical screening population reported to date, providing a more nationally representative assessment of the contributions of Pap and HPV than those previously reported in other cotesting studies.[5,11] The differences in findings between these data and those that served as the primary basis for the ASCCP risk-based management guidelines raise concerns about reliance on a single large integrated health system with characteristics that differ significantly from general US cervical screening practices and population. The ASCCP guideline developers acknowledge that, to ensure that new guidelines are relevant and applicable to the entire US population, data from diverse sources must be analyzed, including screening and follow-up data from national programs that

❚Table 1❚

High-Risk Human Papillomavirus and Liquid-Based (Papanicolaou) Cytology Cotesting Results Preceding Invasive Cervical Cancer Diagnoses, Both Overall and by Specific Histopathology: SCC, ADC, and Other Cervical Carcinomas

Histopathology	Total No.	HPV+, No. (%)	LBC+, No. (%)	Any+, No. (%)	HPV+/LBC+, No. (%)	HPV+/LBC−, No. (%)	HPV−/LBC+, No. (%)	HPV−/LBC−, No. (%)	P Value
All cancers	1,615	1,157 (71.6)	1,189 (73.6)	1,403 (86.9)	943 (58.4)	214 (13.3)	246 (15.2)	212 (13.1)	.15
SCC	939	772 (82.2)	773 (82.3)	865 (92.1)	680 (72.4)	92 (9.8)	93 (9.9)	74 (7.9)	.90
ADC	479	293 (61.2)	286 (59.7)	394 (82.3)	185 (38.6)	108 (22.5)	101 (21.1)	85 (17.7)	.63
Other	197	92 (46.7)	130 (66.0)	144 (73.1)	78 (39.6)	14 (7.1)	52 (26.4)	53 (26.9)	<.0001

ADC, adenocarcinoma or adenosquamous carcinoma; HPV, human papillomavirus; LBC, liquid-based (Papanicolaou) cytology; SCC, squamous cell carcinoma; +, positive; −, negative.

❚Table 2❚

High-Risk Human Papillomavirus and Liquid-Based (Papanicolaou) Cytology Cotesting Results Preceding Precancer Diagnoses, Both Overall and by Specific Histopathology: CIN 3 and AIS

Histopathology	Total No.	HPV+, No. (%)	LBC+, No. (%)	Any+, No. (%)	HPV+/LBC+, No. (%)	HPV+/LBC−, No. (%)	HPV−/LBC+, No. (%)	HPV−/LBC−, No. (%)	P Value
All precancers	11,164	10,343 (92.6)	8,697 (77.9)	10,671 (95.6)	8,369 (75.0)	1,974 (17.7)	328 (2.9)	493 (4.4)	<.0001
CIN 3	10,648	9,882 (92.8)	8,395 (78.8)	10,196 (95.8)	8,081 (75.9)	1,801 (16.9)	314 (2.9)	452 (4.2)	<.0001
AIS	516	461 (89.3)	302 (58.5)	475 (92.1)	288 (55.8)	173 (33.5)	14 (2.7)	41 (7.9)	<.0001

AIS, adenocarcinoma in situ; CIN 3, cervical intraepithelial neoplasia 3; HPV, human papillomavirus; LBC, liquid-based (Papanicolaou) cytology; +, positive; −, negative.

Table 3

High-Risk Human Papillomavirus and Liquid-Based (Papanicolaou) Cytology Cotesting Results Less Than 12 Months vs 12 or More Months Preceding Invasive Cervical Cancer or Cervical Precancer Diagnoses

Histopathology	Total No.	HPV+, No. (%)	LBC+, No. (%)	Any+, No. (%)	HPV+/LBC+, No. (%)	HPV+/LBC–, No. (%)	HPV–/LBC+, No. (%)	HPV–/LBC–, No. (%)	P Value
CxCa									
<12 mo	1,193	925 (77.5)	1,015 (85.1)	1,123 (94.1)	817 (68.5)	108 (9.1)	198 (16.6)	70 (5.9)	<.0001
≥12 mo	422	232 (55.0)	174 (41.2)	280 (66.4)	126 (29.9)	106 (25.1)	48 (11.4)	142 (33.6)	<.0001
CIN 3/AIS									
<12 mo	8,022	7,827 (97.6)	7,165 (89.3)	7,999 (99.7)	6,993 (87.2)	834 (10.4)	172 (2.1)	23 (0.3)	<.0001
≥12 mo	3,142	2,516 (80.1)	1,532 (48.8)	2,672 (85.0)	1,376 (43.8)	1,140 (36.3)	156 (5.0)	470 (15.0)	<.0001

AIS, adenocarcinoma in situ; CIN 3, cervical intraepithelial neoplasia 3; CxCa, cervical cancer; HPV, human papillomavirus; LBC, liquid-based (Papanicolaou) cytology; +, positive; –, negative.

serve all women.[19] KPNC acknowledged the limitations of their population cohort as not meeting this standard due to the geographic limitation of their health plan and the underrepresentation of women of low socioeconomic status.[5-9] The nationwide Quest Diagnostics database used here more closely approaches this standard.

The primary objective of cervical screening is to minimize the incidence of cervical cancer and the morbidity and mortality associated with the diagnosis.[20-22] Therefore, the performance of cervical screening tests over time preceding histopathologic diagnoses of CxCa in previously screened women is of particular interest. A previous large Quest Diagnostics cotesting study of women who had cervical biopsy findings within 1 year of cotesting reported that LBC-positive results preceded 462 (87.8%) of 526 CxCa cases, whereas HPV-positive results preceded 428 (81.4%) of CxCa cases.[23] The current study reports similar results. When taken together, LBC and HPV cotesting identified 94.1% of CxCa cases. These findings support the conclusion that cotesting performs better when identifying cervical cancer than either Pap or HPV testing alone within cotesting.

KPNC reported on 600 cotesting results within less than 12 months of a CxCa diagnosis; 518 (86.3%) of these prior cotests had Pap-positive results, while 535 (89.2%) had HPV-positive results.[5] In contrast, Magee-Womens Hospital (MWH) of the University of Pittsburgh Medical Center reported a higher percentage of LBC-positive cotest results than HPV-positive cotest results; of 109 cotesting results within 12 months from CxCa diagnoses, positive results were found in 99 (90.8%) of LBC cotests and 92 (84.4%) of HPV cotests.[11]

KPNC data yielded markedly different findings from those in the current study and the smaller MWH study; KPNC data showed superiority of HPV testing over cytologic testing within cotesting to identify cervical cancer within 12 months of diagnosis. Both the current and MWH cotesting studies demonstrate the superiority of LBC over primary HPV testing in subsequent 12-month diagnoses of cervical cancer. Furthermore, HPV testing alone missed identifying CxCa 10.8% of the time in the KPNC study compared with 22.5% in the current study. Cytology practices in the different systems have been discussed as one possible factor to explain some of these differences.[11] In relying exclusively on the conventional Pap smear until 2009, KPNC may have been the last large US system to adopt LBC. In contrast, both Quest Diagnostics and MWH used only FDA-approved LBC for cytology testing among all cotested cases, a more reliable method for cytology testing as documented by a Quest Diagnostic–based study in 1999.[24]

All three cotesting studies (Quest Diagnostics, KPNC, and MWH) document that cervical screening was more likely to yield abnormal findings prior to SCC than ADC CxCa diagnoses. Worldwide, cervical screening has proven significantly less able to prevent development of ADC; the chief clinical benefit of cervical screening for glandular neoplasia may be its ability to detect early stage treatable cervical adenocarcinomas when women can still be cured.[25,26] In this study, prior HPV-positive cotest results were more frequently documented prior to SCC diagnoses than prior to ADC diagnoses: 82.2% for SCC and 61.2% for ADC. A clear difference between three cotesting screening studies among ADC CxCa cases was the lower rate of reported cytologic abnormalities prior to all ADC diagnoses reported at KPNC (45.4%)[5] compared with Quest Diagnostics (59.7%) and MWH (73.1%).[11] This may be due to the different screening methods (conventional Pap vs enhanced LBC), as previously noted. These differences underscore the limitations of using only KPNC data as the source for risk projections that were used by ASCCP for creating guidelines..

HPV cotest results were more often positive prior to precancer diagnoses than prior to CxCa diagnoses. Among women with CIN 3, however, available long-term natural history studies indicate that only 30% of CIN 3 lesions progress to invasive cervical cancer in 30 years.[27] Because most CIN 3 lesions will not progress to CxCa,
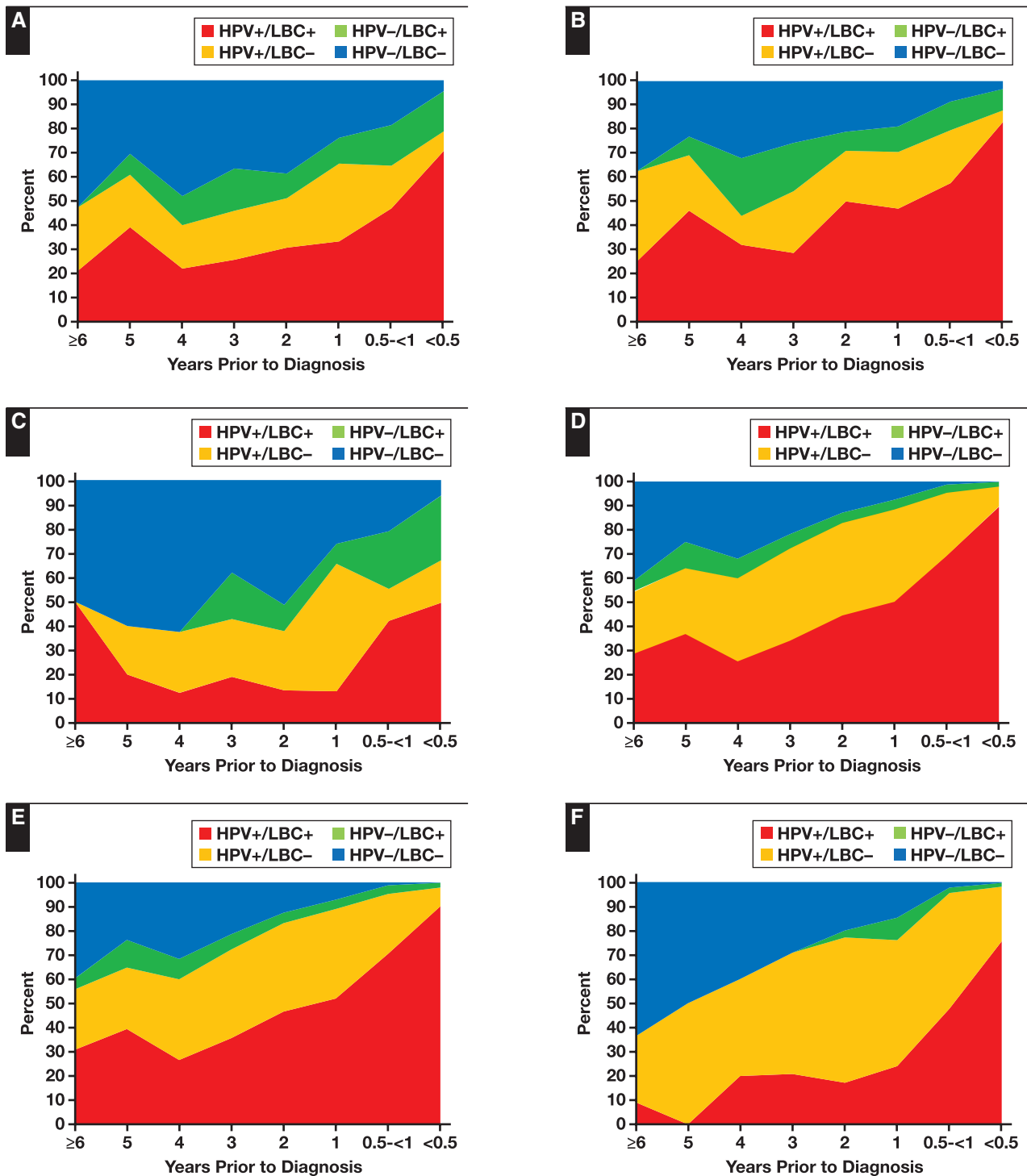
Figure 1 Results of cotesting for various time periods prior to histopathology diagnoses. **A**, All cervical cancers. **B**, Squamous cell carcinoma. **C**, Adenocarcinoma or adenosquamous carcinoma. **D**, Cervical intraepithelial neoplasia grade 3 (CIN 3)/adenocarcinoma in situ (AIS). **E**, CIN 3. **F**, AIS. HPV, human papillomavirus; LBC, liquid-based (Papanicolaou) cytology; +, positive; –, negative.

detection of these nonprogressive lesions does not enhance prevention of invasive cancer and has been termed by some epidemiologists as "over-diagnosis."[28] The only way to measure the relative detection of progressive vs nonprogressive intraepithelial lesions is to specifically measure the number of interval cancers diagnosed between two screens and the cancers detected by the subsequent screen.[28]

The only randomized controlled trial that used this approach in comparing cytology and HPV screening has been a Finnish cervical screening study, in which investigators concluded that the detection of progressive lesions using HPV testing was similar to that of Pap testing but that HPV testing alone caused more diagnoses of nonprogressive lesions ("overdiagnosis").[29] HPV screening excelled in detecting nonprogressive intraepithelial lesions and supplements LBC testing in the detection of CxCa. Overdiagnosis is associated with additional procedures but does not lower cancer risk. In contrast, underdiagnosis is associated with fewer procedures and increases cancer risk.

Accordingly, detection of prevalent "precancers" (detection sensitivity) is likely to overestimate the effectiveness of any screening formulation in preventing invasive cancer. Because of this bias, the performance of screening tests targeting the diagnosis of invasive cancer as the primary end point of screening effectiveness is especially relevant in judging the limitations of available screening options. This view suggests a significant, unrecognized weakness in the ASCCP "risk-based guidelines" calculations that use CIN 3+ as the key measured end point, since most detected lesions in this end point are nonprogressing intraepithelial lesions.[27] The significant differences between the HPV genotypes detectable in invasive cervical cancers compared with HPV genotypes detectable in CIN 3 also reflect the nonprogressive character of many high-grade squamous intraepithelial lesions.[30,31]

This study is limited by including only women who sought medical care and were referred for laboratory services to Quest Diagnostics. However, given the broad representation of patients served by Quest Diagnostics, this is also a key strength of the study. The inclusion of women 30 years and older who had cotesting excluded women who may have been tested with only LBC or HPV. Given that cotesting is currently preferred (not the only standard of care) for these patients, the approach excludes a trivial fraction of testing outside of these practice patterns.

Our findings clearly demonstrate that the rates of positive cervical screening test results (both LBC and HPV testing) decline as the interval between cotesting and CxCa diagnosis increases (Figure 1). Declining rates for positive cervical screening test results prior to CxCa diagnoses are of far greater concern than declining positive rates before precancer diagnoses, because cervical screening primarily strives to prevent cervical cancer and minimize morbidity and mortality.[20-22] This study and all previous large US cotesting studies have shown that both abnormal cytologic and HPV-positive test results

decline progressively as time before CxCa diagnoses increases,[5-7,11,23] most likely due to smaller lesional size and increased difficulty in sampling infected lesional cells. In European trials, HPV-negative rates in women developing incidental CxCa 2.5 to 8 years after the start of trials rose to 42%.[32] Also critically, the risks associated with declining screening test performance before CxCa diagnoses have been obscured by the primary focus of clinical trials on a CIN 3 end point.

The ASCCP proposed "risk-based guidelines" focus on detection of prevalent high-grade intraepithelial lesions rather than CxCa as the primary end point of the screening process. Screening guidelines for a condition as serious as CxCa should be developed based on the most rigorous longitudinal assessment of current technologies applied to a large, heterogeneous, geographically distributed, and socioeconomically diverse population as possible, as such factors represent the conditions under which most care is provided throughout the United States. It is important to reconcile the contrasting conclusions derived from the regional KPNC population, suggesting that HPV primary testing is more effective than cotesting for diagnosing cervical cancer, and the national Quest Diagnostics population findings, which suggest the opposite.

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