correspondence

Cotesting in Cervical Cancer Screening

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To the Editor

We read with great interest the article by Kaufman et al.[1] The authors stated that human papillomavirus (HPV) testing along with cytology (ie, cotesting) was more effective than either Papanicolaou (Pap) cytology alone or HPV testing alone for detecting cervical cancer. This conclusion was based on data from a large reference laboratory that used 2 different HPV assays (Digene Hybrid Capture 2 [HC2; Qiagen] and Aptima HPV RNA assay [Hologic/Gen-Probe]) in routine cervical cancer screening.

As we reviewed the article by Kaufman et al,[1] several themes were either evident or implied:

1. The authors conclude that cotesting is more effective than either cytology-based screening or HPV primary testing within cervical cancer screening programs.
2. This argument is based on the detection of cervical cancer as the clinical end point and relied on real-world data from a large reference laboratory to substantiate this conclusion.
3. The discussion in the article implied that the role of cervical cancer screening was to detect cervical cancer and suggested that detecting cervical intraepithelial neoplasia grade 3 (CIN 3) as a clinical end point would result in "overdiagnosis" during cervical cancer screening.
4. The authors inferred that retrospective, real-world data from a large reference laboratory were more informative than prospective clinical trials and previous data sources used by the National Cancer Institute (NCI), the American Society for Colposcopy and Cervical Pathology (ASCCP) guideline committee, and other medical guideline committees, when formulating the most recent risk-based clinical management guidelines.[2]
5. Several unmentioned issues arise that, we believe, deserve to be highlighted for future discussion:
    a. Implied criticism of the new ASCCP guidelines
    b. Issue of potential erosion of clinician confidence in the ASCCP guideline recommendations or suspicions about the review process that led to the most recent ASCCP management recommendations
    c. Unspoken issue of cost-effectiveness as part of the discussion regarding cervical cancer screening options

The assumption that cotesting finds more cervical cancer than HPV testing alone is based on an incorrect premise. The goal of cervical cancer screening is to detect cervical precancer (CIN 2+), not to detect invasive cervical cancer. The authors appear to minimize efforts to detect cervical precancer in their data analysis and interpretation. In fact, the authors' own data in this article clearly show that HPV testing detects more CIN 3 and adenocarcinoma in situ (AIS) lesions than does cytology. This result is confirmation of previous data from the Kaiser Permanente population cohorts that also demonstrated HPV testing was more sensitive than cytology alone.[3,4]

Numerous randomized controlled clinical trials have demonstrated similar improvements in clinical sensitivity for CIN 2+ disease detection and the prevention of CIN 2+ and cervical cancer development during follow-up screening using HPV testing compared with cytology.[5,6]

If HPV testing is more sensitive than cytology, it might appear reasonable to expect that the combination of both tests (ie, cotesting) would be more sensitive than either test alone. However, this improvement in sensitivity is marginal, as shown in the Kaiser Permanente data.[3,4] Likewise, analysis of residual disease (measured as CIN 2+, CIN 3+, or cervical cancer) following screening has shown that cotesting and HPV primary screening have similar rates of residual disease, indicating that the use of cotesting is essentially equivalent to HPV primary screening in terms of residual risk within the screened patient population.[7]

Collectively, these data point to the same conclusion—namely, HPV testing is more sensitive than

cytology-based screening, and the inclusion of cytology along with HPV testing provides little benefit in terms of improved sensitivity or diminution of longitudinal risk than that provided by HPV testing alone. In comparison to the use of HPV primary screening, cotesting has been shown to increase the number of tests performed,[6] the number of referrals to colposcopy,[7,8] and the cost of testing,[8] while providing little reassurance of increased protection against future cervical precancer compared with the use of HPV testing alone as the primary screening method.[7]

A topic that was not addressed but requires a brief comment is that of cost-effectiveness. Cotesting is a viable option, as is cytology-based screening or HPV primary screening. The current screening and management guidelines support all 3 options. The clinical evidence is moving toward HPV primary screening, which is both clinically effective and cost-effective. The ultimate decision about the use of cotesting should be based on a patient's comfort level, the advice of her clinician or health care provider, and the ability of the patient and the health care system to afford the cost incurred with the use of 2 screening tests (cotesting) vs a single screening test (HPV test, followed by reflex cytology testing for the HPV-positive patents). Although cervical cancer screening and management guidelines are based on the quality of the clinical evidence, laboratories, clinicians, and patients are also cognizant of the cost and reimbursement concerns regarding cervical cancer screening options. Economic modeling studies from both the Netherlands and the United States have reported that HPV primary screening is more cost-effective than cytology-based screening methods or cotesting.[9,10]

We believe that cost will continue to remain a silent but important issue within cervical cancer screening programs in the United States.

The assumption of the article's authors, that cervical cancer is the major clinical end point for the general screening population, seems surprising to us. The point of cervical cancer screening is to detect and treat precancer in order to prevent the development of cervical cancer. We are reminded of an approach taken in New Zealand in which women with cervical carcinoma in situ were not treated. The results of this tragedy were immeasurable for the affected patients and their families, and confidence in the New Zealand medical community was eroded.[11,12]

The science behind the natural history of cervical carcinoma is quite clear. The vast majority of both cervical squamous cell carcinomas and adenocarcinomas arise from a persistent high-risk HPV infection. This persistent infection gives rise to well-defined precancerous lesions (high-grade squamous intraepithelial lesion, CIN 3, AIS) that precede the development of cervical cancer.[13]

It is recognized that not all CIN 3 lesions will progress to cancer; many will regress. The problem is that a clinician cannot distinguish between progressive and nonprogressive CIN 3 lesions at the time of colposcopy. As such, the prudent course of medical practice is to detect all CIN 3 lesions and to remove them before any can develop into invasive cervical cancer. The effective use of cervical cancer screening technologies based on the detection of CIN 3, which is backed by rigorous review of the clinical evidence and forms the basis of effective screening and management guidelines, provides assurance to both clinicians and patients that the most effective screening methods are used to prevent the development of invasive cervical cancer.

It is interesting to note that within their article, Kaufman et al[1] reported their data showing that HPV testing, not cytology, detected the majority of CIN 3 and cervical AIS cases—the same result published previously by the NCI using the Kaiser Permanente data.[2]

On the assumption that guideline committees should use real-world data and not be overly reliant on data from a single institution to develop and revise cervical cancer screening guidelines, several points should be considered. First, we agree that all available data should be reviewed, scrutinized, and then analyzed to synthesize the most effective cervical cancer screening and management guidelines. This process is based on clear understanding of the screening technologies and the inclusion and exclusion criteria used in the case selection that goes into the data analysis.

The data used by Kaufman et al[1] raises several questions that are difficult to resolve based on the information provided. First, the authors report that 2 HPV assays (HC2 and Aptima) were used with liquid-based cytology (LBC) specimens (PreservCyt and SurePath) to generate the data presented in the article. However, some of these testing methods not approved by the US Food and Drug Administration (FDA; ie, the FDA has not approved the use of HC2 or Aptima with SurePath LBC specimens in cervical cancer screening). The authors did not report on the clinical validation studies to show that the off-label use of these cervical cancer screening methods was equivalent to the performance of the FDA-approved methods. In addition, the authors did not separate the data for FDA-approved and off-label use of screening technologies. As such, the reader does not know if the data should have been pooled and analyzed together (as was the case in the article) or if the data

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sets should have been analyzed separately—one for the FDA-approved testing methods and the other for the off-label testing methods. Without such an analysis, it is not clear how the data published by Kaufmann et al could be used to influence individual clinician choices about screening options and how the same data can further influence guideline committees on the appropriate use of screening technologies within cervical cancer screening methods. It is unfortunate that the data did not include the use of HPV assays that are FDA approved with SurePath LBC—namely, Roche cobas and BD Onclarity—which would have avoided the issue of on-label vs off-label use of HPV testing.

The article by Kaufman et al[1] did not describe case inclusion and exclusion criteria, the screening duration times, follow-up methods, and so forth. These factors potentially create bias in how the data were assembled and presented to the reader. Moreover, their analysis was limited to 9,307 patient results (1,259 cancers and 8,048 CIN 3 or AIS lesions) from a total of 18,832,014 cotest results generated during the study period, or just 0.05% of the total available data.

Lack of patient demographics and screening history is an issue that should have been defined within the article. Knowledge of the screening history for the patients that were included vs the patients who were excluded from the analysis should have been detailed. Hypothetically, if a disproportionate number of people with HPV-positive screening results were treated at some point and not included in this analysis, that could affect the final cancer results with respect to HPV status. Without such data or explanation, it is difficult for the reader to understand which data sets can be pooled, which data should be analyzed separately, and which data should be excluded from the analysis, and to ascertain and evaluate the various sources of bias that could have affected the authors' overall conclusions.

With respect to the unspoken issues related to the implied criticism of the new ASCCP guidelines, we offer the following perspective. As practitioners of systematic literature reviews, real-world data analysis, and clinical evidence synthesis, we have the utmost respect for data sources and analyses published by the NCI; the rigorous literature review that goes into the US Preventive Services Task Force cervical cancer screening recommendations; and the subsequent review, synthesis, and recommendations made by the guideline committees, whether the committees are associated with the ASCCP, the American Cancer Society, the American College of Obstetricians and Gynecologists, or the Society for Gynecologic Oncology. Transparency and intellectual integrity are abundantly demonstrated throughout the process. Kaufmann et al[1] seek "to reconcile the contrasting conclusions derived from the regional KPNC [Kaiser Permanente Northern California] 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" and suggest that their data are more representative of the US population as a whole. However, this characterization is not accurate. The 2019 ASCCP management guidelines are not based on only the KPNC population: "several additional databases were analyzed to ensure that results are applicable to patients of diverse racial, ethnic, and socioeconomic strata. Risk estimates were compared using screening and follow-up data from clinical trials (BD Onclarity registrational trials), a state registry (New Mexico HPV Pap Registry), and the Centers for Disease Control and Prevention's (CDC's) National Breast and Cervical Cancer Early Detection Program, a national program that includes many low-income and minority patients."[2]

Regarding the potential erosion of clinician confidence with the new ASCCP guideline recommendations or suspicions about the review process that informs the updated screening and management recommendations, we believe that all relevant information should be reviewed and analyzed within the context of current cervical cancer screening and management guidelines. As new information becomes available, such ongoing data review and analysis should not detract from the intellectual integrity that forms the foundation of our cervical cancer screening and management guidelines.

Finally, the American Cancer Society recently published its updated cervical cancer screening guidelines for 2020.[14] These updated guidelines clearly indicate that cervical cancer screening should begin at age 25 with the use of HPV primary screening as the preferred screening method. Cotesting is considered acceptable if HPV primary screening is not available. Based on the strength of the evidence published by the American Cancer Society and the ASCCP, we fully endorse these new guidelines on cervical cancer screening and management.

We look forward to ongoing discussion of this topic as we continue to advance the impact of cervical cancer screening programs.

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The Authors' Reply

We appreciate the interest and considerate response of Malinowski and colleagues to our large, nationwide, real-world findings on cytology and HPV cotesting data.[1] Many issues are raised in their comments, and, like these authors, we agree about the importance of ongoing study and evaluation as data continue to emerge in response to changes in practice patterns and disease dynamics.

We concur with the importance of detecting cervical cancer and precancerous lesions; both require appropriate evaluation and management. We do not discount the contributions from identifying and treating precancerous lesions in reducing morbidity and mortality from cervical cancer. We focused our discussion specifically on the differential detection of cancer because it is the primary disease state that all screening approaches seek to avoid.[2] As with all aspects of laboratory medicine, no test is perfect, and tests must be ordered and interpreted in the appropriate circumstances.

Among cotested specimens, in our study, the HPV component alone did not identify 45% (190/422) of evolving cervical cancers more than 12 months before their diagnoses.[1] This deficiency is of grave concern. By endorsing primary HPV screening once every 5 years, some women will escape cervical cancer detection who would otherwise have been detected using the cotesting approach. We agree that the inclusion of primary HPV screening as an option in guidelines may afford screening access to individuals unable to afford cotesting, something that has been demonstrated in resource-limited countries and in some European countries.[3,4] We have taken a medical risk-benefit approach, excluding cost, and find that there will be women with cervical cancer whose condition would be detected using cotesting who would be missed with primary HPV testing alone. In one study, more than 1 in 3 women who had CIN 2 or 3 and/or carcinoma would have been missed without the Pap cytology.[5] In another study, more than half of the women with CIN 2+ lesions including cervical cancer had a positive Pap test and negative HPV testing.[6] Regarding costs, Felix et al examined cost-benefit and found that, compared with primary HPV screening, cotesting both saved lives and was cost-effective.[7] Our and other findings raise questions about establishing primary HPV screening as the preferred option at present and eliminating the option of cotesting as part of cervical cancer screening guidelines, as suggested recently by the American Cancer Society.[8]

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Women with both negative HPV and cytology are less likely to develop CIN 3+. In the KPNC study, these women were at 16% lower risk than those who were HPV negative alone (3.2 vs 3.8 per 100,000 women per year).[9,10] The differences observed between our analysis and the similar KPNC data analysis raise questions about the generalizability of regional findings to national guidelines. The discrepancy needs further evaluation before adoption of new guidelines. Likewise, we are concerned about the very different findings from the US Preventive Services Task Force (USPSTF) 2012 and 2018 studies, showing a 7-fold difference in the 5-year risk of developing cervical cancer.[11,12] Among the 25 USPSTF studies incorporated into that analysis, 84% used conventional Pap tests and 48% were from "developing countries"; only 2 were based on US data. Guidelines should rely on diverse clinical and laboratory studies that are directly applicable to current cervical cancer screening practices.

Finally, guidelines must recognize that the rate of progression from neoplasia to cervical cancer is variable. Although disease progression is slow in most women, rates of CIN 3 progression to invasive cervical cancer were 1.6% within 2 years, 2.6% within 5 years, and 9.9% within 10 years.[13] Studies must examine the distribution of the negative to invasive cancer progression rate, addressing consequences for the women who would be missed when models focus on calculated average risk rather than observed risk distribution.

We very much appreciate the expanded dialogue our large national study has engendered. To support effective test utilization, we hope that the contributions of various types of scientific studies and data will be evaluated together as diagnostic approaches aimed at reducing the incidence and consequences of cervical cancer evolve. Working together, we will continue to strengthen the guidelines of the American Society for Clinical Pathology, the American Society for Colposcopy and Cervical Pathology, the American Cancer Society, the American College of Obstetricians and Gynecologists, and other stakeholders. We wholeheartedly support these efforts and look forward to being part of the discourse.

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