Comparison of Cervical Cancer Screening Results Among 256,648 Women in Multiple Clinical Practices

Blatt et al[1] have presented data regarding the correlations of routine high-risk human papillomavirus (HPV) and Papanicolaou (Pap) "cotesting" results with biopsy diagnosis in approximately one-quarter of million women aged 30 to 65 years. These data complement those from Kaiser Permanente Northern California, in which >1 million women aged 30 to 65 years have been cotested since 2003.[2]

Unfortunately, the analysis by Blatt et al[1] introduces a bias that favors disease detected by Pap testing and, by extension, cotesting. Guidelines recommend that women who have an HPV-positive atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesion, or more severe cytologic interpretation are referred for immediate colposcopy.[3] Women who test positive for HPV but have a negative Pap test (HPV+/Pap−) are recommended to undergo rescreening within a year and sent to colposcopy if they have a cytologic abnormality or evidence of persistent high-risk HPV.[3]

Thus, including only those women who underwent a biopsy within 1 year excludes a significant percentage of women with HPV+/Pap− results who came back for rescreening, because many women do not come back exactly at 1 year (or less) but return over the course of several months past the one-year anniversary. Restricting to 1-year follow-up likely results in an underattribution of disease detected by HPV screening and missed by Pap testing. It therefore will be important to reanalyze these data with ample follow-up of the women with HPV+/Pap− results to better reflect the real-world performance of HPV testing and cotesting.

More importantly, the critical question should be what cervical cancer screening strategy is more effective and cost-effective, and has a better benefits-to-harms ratio over a "screening lifetime." Although a single cotest will always be more sensitive than either test alone, how does cotesting every 5 years compare with HPV testing alone every 3 or 4 years projected over 20 or 30 years? For example, over a 20-year period, are 4 rounds of cotesting every 5 years more effective than 5 rounds of HPV testing alone every 4 years? Recent data from Kaiser Permanente Northern California[2] have demonstrated that the 5-year reassurance after a negative cotest is approximately the same as the 4-year reassurance after a negative HPV test. Cotesting every 5 years would have one fewer HPV test but 4 more Pap tests than HPV testing every 4 years to achieve approximately the same level of effectiveness in that period of time. Over a 30-year period, cotesting every 5 years would have 4 fewer HPV tests but 6 more Pap tests and possibly less reassurance than HPV testing every 3 years. Thus, screening modalities must be projected over the screening lifetime to estimate its relative programmatic benefits, harms, and costs to make an informed decision regarding which approach is best for women.

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CONFLICT OF INTEREST DISCLOSURES
Dr. Castle has received commercial human papillomavirus tests for research at a reduced or no cost from Roche, Qiagen, Norchip, Arbor Vita Corporation, BD, and mtm. He has been compensated financially as a member of a Merck Data and Safety Monitoring Board for human papillomavirus vaccines. Dr. Castle has been paid as consultant for BD, Gen-Probe/Hologic, Roche, Cepheid, ClearPath, Guided Therapeutics, Teva Pharmaceutics, Genticel, Inovio Pharmaceuticals, and GE Healthcare. Dr. Castle has received honoraria as a speaker for Roche and Cepheid.

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Reply to Comparison of Cervical Cancer Screening Results Among 256,648 Women in Multiple Clinical Practices

We appreciate Dr. Castle's interest in our recent article,[1] which evaluated 8.6 million women screened for cervical

cancer in >10,000 clinical practices. Our intent was to elucidate the real-world performance of screening options for biopsy-proven cervical intraepithelial neoplasia of grade 3 and cancer in women aged 30 to 65 years, recognizing that adherence to guidelines in cervical cancer screening is incomplete.[2]

The advantage of our study compared with the ATHENA (Addressing the Need for Advanced HPV Diagnostics) trial[3,4] and the Kaiser Permanente study[5] is that it better represents true clinical practice. Because our study included women in whom a biopsy was preceded by a Papanicolaou test and human papillomavirus (HPV) test, our patient population was composed of women presenting for rescreening as well as screening that might be outside of recommended guidelines. Thus any bias, as suggested by Dr. Castle, is mitigated. Bias would also be mitigated by the fact that nearly equal numbers of women with negative Papanicolaou test results (66,478 women) and HPV-negative test results (64,870 women) were evaluated.

We agree with Dr. Castle that the risks and benefits of cervical cancer screening should be evaluated over a "screening lifetime." The small number of cancer cases (8 cases) identified in the ATHENA trial limits its use in assessing lifetime cancer risks. The Kaiser Permanente study,[5] in which >400 cervical cancer cases were identified, offers a more robust data set for such analysis. It demonstrated a statistically significant increase of 57% in the 3-year cumulative risk of cervical cancer associated with a negative HPV-only test (0.11%) versus a negative cotest (0.07%) (P=.03).[6] Understanding how this increased risk observed with a one-time HPV-only test will translate into lifetime risk is important before new screening guidelines are adopted.

In our study, HPV-only testing missed 98 of 526 cervical cancers (18.6%), which is significantly more than were missed by cotesting (29 cancers; 5.5%) (P <.0001).[1] In this context, it is important to note that verification bias is a limitation of all routine clinical practice cancer screening data sets that tends to increase the apparent sensitivity of the screening tests, including HPV-only and cytology.[7] Therefore, our results[1] could actually be an understatement of the risk inherent in HPV-only testing.

Finally, we agree with Dr. Castle that a single cotest will be more sensitive and provide a higher level of protection from future disease than either test alone. Our real-world study supports cotesting as the most effective cervical cancer screening method for women aged 30 to 65 years.[8,9]

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CONFLICT OF INTEREST DISCLOSURES

Drs. Blatt, Rabin, Kennedy, and Luff are full-time employees of Quest Diagnostics.

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