

Editorial

See related article by Dijkstra et al., p. 55

Positive High-Risk HPV Test with Negative Cytology— A Conundrum and Blessing of Our Latest Technology

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The POBASCAM trial (1) was one of the earliest and longest randomized controlled trials to address the test performance of high-risk HPV (hrHPV) testing to detect cervical precancerous lesions. It builds on the evidence presented in HART (2). Of importance is the 29-year-old starting age for study enrollment. The European cohort study (3) included younger women starting at 20 years from Denmark, France, and Spain. The US industry-sponsored ATHENA cohort trial started at 21 years (4). Most trials showed that the prevalence of hrHPV is highest in those younger than 30 years and lowest between 35 and 54 years of age, after which it increases again (5).

The United States has recently moved the age to start screening up from 3 years after initiation of sexual intercourse to 21 years (6–8), which has omitted all of the adolescent and early-college health screenings. These recommendations are strongly supported by the evidence, but acceptance by both health-care professionals and women has been slow (9). Much of the Western world has adopted screening initiation at age 30. Age of the woman screened is highly related to the efficiency of the screening test used.

Dijkstra and colleagues (10), as well as other screening HPV testing studies (3, 4), have shown that positive hrHPV testing immediately triaged with cytology results in a specificity of above 50%, the threshold at which the chance of ruling in cervical intraepithelial neoplasia (CIN) grade 3 or worse (CIN 3⁺) disease is a coin flip. This management strategy results in the fewest referrals to colposcopy (31%), but the lowest detection of CIN 3⁺ disease (10). By adding HPV 16/18 genotyping to the cytology triage test, Dijkstra and colleagues showed that the detection of CIN 3⁺ improves significantly, but at a large cost of sending more than half of the population to repeated testing and colposcopy. This calls cost-effectiveness into the discussion.

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Cost-effectiveness models show that triennial screening strategies between 21 and 30 years of age are most cost-effective when atypical squamous cells of undetermined significance (ASCUS) cytology is followed by high-risk HPV testing among unvaccinated women, increasing the interval to every 5 years for vaccinated women (11).

For women 30 years and older, several cost-effective strategies have been identified: in increasing order of incremental cost-effectiveness ratio for quality-adjusted life years (11), screening every 5 years among unvaccinated women with cytology followed by hrHPV testing for ASCUS; screening every 5 years among unvaccinated women with hrHPV testing followed by cytology for positive hrHPV; screening every 5 years among vaccinated women with cytology followed by hrHPV triage; screening every 5 years among vaccinated women with hrHPV followed by cytology triage; and, finally, screening every 3 years among unvaccinated women with hrHPV followed by cytology triage. There is no cost-effective strategy for screening vaccinated women 30 years and older at a 3-year interval (11); nor does cotesting with hrHPV and cytology in women 30 years and older minimize testing and colposcopies (12). Cost-effectiveness analyses at the same level of sophistication as has been done with the cytology and hrHPV testing are lacking for cytology and HPV 16/18 genotyping triage after an hrHPV test (13).

The study by Dijkstra and colleagues includes an additional triage step to minimize false-positive results by testing women again at 6 months. These data indicate that a positive hrHPV test among women 30 years and older with a normal cytology triage test followed by cytology again at 6 months is the only triage test examined that provides a specificity of above 50%. The addition of HPV 16 or 16/18 genotyping to the immediate triage increases detection to 100%, but at great cost to the increased numbers of tests and colposcopies ensuing for the false-positive women.

The United States would be well served by studying the results of the Dijkstra and colleagues work. Using a triage strategy after hrHPV testing is less expensive in dollars and numbers of women referred to colposcopy who are falsely positive than is the cotesting strategy put forth by the recent American Society of Colposcopy and Cervical Pathology (ASCCP) management guidelines change (14, 15). With the strong evidence from POBASCAM and other trials, the screening strategies for cervical cancer in the United States should evolve to an older age of initiation as well as a triage testing scheme rather than cotesting strategies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Conception and design: D.M. Harper

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