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In 1941, Dr George Papanicolaou and Dr Herbert Traut published a landmark study concerning a new diagnostic test for the early detection of cervical cancer (1). This test became commonly known as the “Pap smear.” This screening test was responsible for a remarkable decrease in cervical cancer mortality in well-screened populations, with an approximately 80% decrease in the United States in the second half of the 20th century. Despite its value as a cancer prevention tool, the Pap smear has several well-known shortcomings. Cytological screening for cervical dysplasia and cancer requires infrastructure and training for the collection and interpretation of samples. The Pap smear is also less than 100% sensitive for the detection of clinically significant premalignant cervical disease. This problem requires that the test be repeated at frequent intervals. Diagnostic testing for human papillomavirus (HPV) infection has emerged as an alternative to the venerable Pap smear. Multiple publications over the past decade have demonstrated the sensitivity of the HPV test for the detection of cervical dysplasia and cancer. In one study in rural India (2), one round of HPV testing was superior in reducing cervical cancer mortality when compared with the Pap smear.

The optimal clinical strategy for the use of HPV testing is not clear at this point. The shortcoming of the HPV test is its poor positive predictive value—most women with a positive HPV test do not have cervical dysplasia or cervical cancer. Persistent HPV infection is an intermediate step in the development of cervical neoplasia. A majority of HPV infections are cleared without clinical disease. Persistent HPV infection leads to continued expression of the HPV viral oncogenes E6 and E7, with the subsequent development of cervical disease. This process takes years. In this issue of the Journal, Chen et al. (3) examine the value of repeated HPV testing. These investigators studied approximately 10,000 women in Taiwan, and these subjects were followed over 16 years. Persistence of HPV infection—defined by two positive tests spaced 2 years apart—was associated with a 2- to 10-fold elevation in risk of cervical carcinoma in situ or cervical cancer compared with a single positive HPV test. There are several notable strengths to this study, including a long duration of follow-up, a large sample size, and linkage to a national cancer registry. The investigators also demonstrated the utility of type-specific testing in identifying persistent infection. Specifically, they identified HPV16, HPV52, HPV58, HPV18, and HPV31 as the virus types most commonly associated with later development of cervical cancer. Their findings suggest that HPV testing at 2-year or longer intervals would identify a specific subset of women with persistent HPV infections, who are at greater risk for cervical dysplasia and cervical cancer. This study also demonstrates that women with negative HPV test results have a lesser risk of cervical disease, and this decrease extends years beyond the initial negative screening.

Primary prevention of cervical cancer is a realistic strategy for the 21st century since the introduction of HPV vaccines 5 years ago. Modeling has been an important tool to evaluate HPV vaccination policy and cost-effectiveness. In this issue of the Journal, Goldie and Daniels (4) use a known model (5) of cervical cancer outcomes and introduce health disparities into these simulations. This modeling study includes both cost-effectiveness and clinical outcomes. In their introductory comments, the authors point out the multiple reasons for disparities in cervical cancer mortality in the United States. Modeling of racial and ethnic subgroups at increased risk identifies strategies that can reduce cancer burden within these groups. HPV vaccination can reduce cervical disease due to HPV16 and HPV18, and prior studies have demonstrated a decrease in cervical dysplasia in vaccinated women (6,7). These benefits have become evident in a “real-world” population-based study from Australia (8). Goldie and Daniels study (4) suggests that the benefits of vaccination can potentially be distributed equitably across racial and ethnic groups, and they identify interventions for subgroups such as increased screening and the use of the more sensitive HPV test as strategies that both improve clinical outcomes and reduce health disparities. The authors refer to these interventions as a “win-win” scenario, with substantial reductions in cervical cancer mortality across all subgroups of women and narrowing the gap in cervical cancer disparities.

In summary, Dr Papanicolaou’s test to identify cervical cancer and associated precursor lesions has had a remarkable run of reducing cervical cancer mortality for many decades. However, recent medical research has identified HPV vaccination and HPV diagnostic testing as potential improvements on the Pap smear. These improvements should be available to all women.

References


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