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The Changing Face of Cervical Cancer Screening in the United States

Warner K. Huh, MD

With the introduction of widespread Pap smear screening starting in the 1940s, the United States has seen at least a 50% reduction in the incidence and mortality of invasive cervical cancer. In light of the ease of sampling, the long pre-malignant phase of cervical cancer, and well-tolerated treatment options for pre-invasive disease, cervical cancer screening has served as a model for screening for other malignancies.

For some women, it also serves as the cornerstone for annual routine visits with gynecologists. Both patients and gynecologists have been taught that a yearly Pap test is important, and it can serve as the backbone of care. Unfortunately, however, access to screening and treatment for cervical cancer continues to be an issue for some women in the United States. Approximately 60% of women with invasive cancer had not undergone a Pap test in the 5 years preceding their diagnosis or have never undergone a Pap test.¹

The long history of Pap tests has also taught us a number of lessons. We have learned that cytologic screening is hardly perfect. In a study by Nanda et al.² the sensitivity of a single test was 51%, and this was subsequently confirmed in a pooled analysis of European and Canadian studies by Cuzick et al.³ One way to compensate for this poor sensitivity is by using serial screening; the sensitivity of cytology increases to 76% with 2 consecutive annual Pap tests and 88% with 3 consecutive tests.

Just adding tests and procedures, however, is not always the answer, and most recently the pendulum has swung in the other direction. We now understand the risk of overtreating pre-invasive disease and the potential impact of overtreatment on preterm labor and neonatal morbidity and mortality. In many adolescents and young women, abnormal Pap tests and underlying disease will resolve spontaneously. Therefore, in 2009, the American College of Obstetricians and Gynecologists recommended that screening for cervical cancer start at age 21.⁴

Another lesson learned is the role of human papillomavirus (HPV) in cervical cancer. High-risk (HR) HPV DNA testing has become a mainstay of cervical cancer screening over the past 10 years. Experts now recognize that more than 99% of all invasive cervical cancers are associated with 14 different HR HPV types. Currently, HR HPV testing is recommended for women with equivocal Pap tests (ASC-US) and atypical glandular Pap tests (AGC). Most importantly, it is also widely recommended in conjunction with Pap testing in women older

than 30 years of age. In keeping with the lesson of not overtreating and overscreening, after negative Pap and HPV test results, an individual woman can increase her screening interval to every 3 years.

Another benefit of HR HPV testing is its much higher sensitivity than Pap testing (96% vs. 53% in pooled estimates). Since 2005, 7 randomized controlled trials^{5–11} have been published that evaluated HPV testing in the screening setting. These studies have largely shown improvements in the detection of pre-invasive lesions either alone or in conjunction with Pap testing. Of particular note, a recently published trial from Finland showed an advantage with the strategy of HPV followed by Pap testing.⁹ This may represent the best screening strategy for the future.

These lessons lead to another question: given the improved sensitivity of HR HPV testing, why don't we use this test as the primary screening modality in the United States? Almost all clinical screening scenarios use the most sensitive test first, but cervical cancer screening today falls outside this paradigm.

Furthermore, the role of screening may likely change in an HPV vaccinated population. Many fully anticipate that, as the prevalence of cervical abnormalities decrease with increasing rates of vaccination, the performance of screening tests, including Pap testing (specifically the sensitivity and positive predictive value) will further decline. I doubt these compounded losses can be overcome with heightened quality control and computerized imaging systems. This further supports the concept of using a non-subjective test with a high inherent sensitivity such as HPV DNA testing as an initial screening tool.

Undoubtedly, the length and interval of cervical cancer screening will slowly evolve in the United States, and cost-effective strategies that incorporate both screening and vaccination must be and will be carefully reviewed. The National Institutes of Health, the American Society of Colposcopy and Cervical Pathology, and the American Cancer Society are sponsoring the Practice Improvement in Cervical Screening and Management (PICSM) conference in 2011 to address these very issues.

I fully anticipate significant changes in cervical screening and prevention in the next 20 years. We may live in an era in which Pap smears become medical history. Although I once would have thought that impossible, as a gynecologist and oncologist, the current evidence and data are very compelling. Now I would not be surprised if Dr. Papanicolaou himself agreed.

Biography

Warner K. Huh, MD

Warner K. Huh, MD, is Professor in the Department of Obstetrics and Gynecology, Division of Gynecologic Oncology at the University of Alabama at Birmingham (UAB) and a Senior Scientist in the UAB Comprehensive Cancer Center. Dr. Huh's research interests include vaccines for cervical neoplasia and the development of novel screening and treatment strategies for gynecologic malignancies. He has authored or co-authored more than 95 articles, including publications in the *Journal of the National Cancer Institute*, *Cancer*, *Clinical Cancer Research*, *Gynecologic Oncology*, and *Obstetrics & Gynecology*. He is the recipient of an R01 research grant from the National Institutes of Health/National Cancer Institute and an American Cancer Society Research Scholars Grant. He is co-leader of several projects and sits on the steering committee of the Johns Hopkins-UAB Cervical Cancer Specialized Programs of Research Excellence (SPORE) program.

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