Cervical Cancer Prevention

Immunization and Screening 2015

Lauren Thaxton, MD, MBA, Alan G. Waxman, MD, MPH*

KEYWORDS

• Cervical cancer screening • Human papillomavirus • Cytology • HPV vaccine

KEY POINTS

- Immunization against 4 types of human papillomavirus (HPV) is now recommended for girls and boys aged 11 to 12, with catch-up vaccination up to age 26.
- The 2012 screening guidelines recommend either cytology or cotesting with cytology plus a high-risk HPV test.
- The negative predictive value of cotesting is high enough to extend the interval between screening tests to 5 years.

INTRODUCTION

Worldwide, approximately half a million new cases of cervical cancer are diagnosed per year, almost half of which are fatal. The burden of disease is highest in developing countries where cervical screening and immunization are not readily available. In the United States, where screening for cervical cancer has been routine for more than 50 years, cervical cancer is uncommon, with only 12,360 new cases and 4,020 deaths estimated for 2014.[1] Approximately half of newly diagnosed cases of invasive cervical cancer are in women who have never been screened.[2] It is now well established that human papillomavirus (HPV) is the necessary agent in the pathogenesis of cervical cancer. This virus is present in 99.7% of all cervical neoplasms,[3] including essentially all squamous cell cancers and adenocarcinomas. Worldwide, HPV has also been associated with a significant proportion of cancer in sites beyond the cervix, including the anus (88%), vulva (43%), penis (50%), vagina (70%), and oropharynx (13%–56%).[4]

HPV is a double-stranded, encapsulated DNA virus. There are more than 100 types of HPV, at least 40 of which are known to infect the human genital tract and 15 are potentially oncogenic.[5] Ninety percent of cervical cancers worldwide are caused by just 9 types with types 16 and 18 responsible for two-thirds to three-quarters of cases.[6]

Department of Obstetrics and Gynecology, 1 University of New Mexico, MSC 10 5580, Albuquerque, NM 87131, USA
* Corresponding author.
E-mail address: awaxman@salud.unm.edu

Med Clin N Am 99 (2015) 469–477
http://dx.doi.org/10.1016/j.mcna.2015.01.003 **medical.theclinics.com**
0025-7125/15/$ – see front matter

PRIMARY PREVENTION: THE HUMAN PAPILLOMAVIRUS VACCINES

In 2006, the Food and Drug Administration (FDA) approved the first vaccine against HPV, Gardasil. In premarketing studies, Gardasil showed a high level of protection against cervical, vulvar, and vaginal lesions caused by 4 HPV types: 6, 11, 16, and 18.[7,8] In 2009, a bivalent vaccine, Cervarix, was approved by the FDA to target cervical intraepithelial neoplasia caused by HPV types 16 and 18.[9] The efficacy of both these vaccines is very high if given before initial exposure to the virus.[8,9] Gardasil has subsequently been approved for prevention of anal intraepithelial lesions in both male and female patients. The Advisory Committee on Immunization Practices (ACIP) and major professional organizations, including The American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics, recommend routine 3-dose vaccination at ages 11 to 12 (ie, before the onset of intercourse). Gardasil is approved for use in male and female patients, Cervarix for female patients only. Immunization may given to children as young as age 9 and those who have not completed the full 3 doses may be vaccinated up to age 26.[10,11] In December 2014, the FDA approved Gardasil 9, a vaccine that protects against the four HPV types in Gardasil, plus types 31, 33, 45, 52, and 58. These five HPV types in addition to HPV types 16 and 18, are responsible for 90% of cervical cancers.[6] At the time of this writing, the ACIP has not yet issued recommendations regarding this new vaccine.

SCREENING FOR CERVICAL CANCER

In 1941, George Papanicolaou and Herbert Traut[12] published a clinical trial demonstrating the value of the cytology test for cervical cancer.[12] Over the next 2 decades, clinic-based and community-based demonstration projects of the Papanicolaou (Pap) test showed both a decline in invasive cancer and general acceptability of the test to the women to be screened.[13] Since that time, screening recommendations regarding onset and frequency of screening have changed many times as our understanding of the pathogenesis of cervical cancer and the performance characteristics of available screening tests has expanded. Additionally, novel technologies, such as liquid-based cytology and HPV testing, have been developed.

Why Add Human Papillomavirus Testing to the Papanicolaou Test?

Although the widespread use of cervical cytology in the United States has been accompanied by a marked decline in cervical cancer incidence, the sensitivity of a single Pap test to identify cervical intraepithelial neoplasia (CIN) grade 2 or worse is limited, and estimated in several studies between 51% and 55%.[14–16] Moreover, the interreviewer reliability of the Pap test is low, on the order of 50% to 78%.[17] In addition, cytology is poor at detecting adenocarcinoma.[18] The Pap test has worked as well as it has despite the poor sensitivity of a single test because it is repeated periodically during the span of a woman's lifetime. Studies have shown a cumulative risk of CIN3 or worse of 0.17% to 0.50% 3 years after a negative cytology without reference to previous screening.[18–20]

Testing for HPV is now readily available, and studies have consistently shown that testing for HPV has a higher sensitivity and a higher negative predictive value compared with cytology alone.[21] Increased sensitivity, however, comes at a cost of lower specificity.

Katki and colleagues[18] analyzed the course of more than 300,000 women in the Kaiser Permanente Northern California (KPNC) system who were screened with cytology plus an HPV DNA test. In this study, abnormal cytology alone identified a cumulative incidence of CIN3 or worse of 4.7% over 5 years. The cumulative incidence