Cervical Cancer Screening in Immunocompromised Women

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KEYWORDS

- Cervical cancer screening • HIV or AIDS • Solid organ transplant
- Combined antiretroviral therapy

KEY POINTS

- Immunocompromised women are at an increased risk of squamous intraepithelial lesion (SIL) and cervical cancer.
- There is an increased risk of oncogenic and nononcogenic human papillomavirus (HPV) infection, infection with multiple HPV subtypes, and persistence of HPV infection in human immunodeficiency virus–infected women.
- The effect of combined antiretroviral therapy on HPV infection and rates of cervical cancer is inconclusive.
- Vigilance in screening for SIL and cancer in immunocompromised women is warranted.

INTRODUCTION

Immunocompromised women encompass a variety of populations, the largest being human immunodeficiency virus (HIV)–infected women. Approximately 17 million women worldwide are HIV-infected, with US estimates at 280,000.[1,2] Women who belong to the other immunocompromised populations are solid organ transplant recipients and patients with conditions requiring chronic immunosuppressive therapies such as systemic lupus erythematosus (SLE), inflammatory bowel disease (IBS), and other conditions requiring chronic immunosuppressive therapies. Cervical cancer screening in these populations has been debated and insufficiently investigated except in the HIV-infected population. Limited numbers of studies and conflicting data have made it challenging to develop evidence-based guidelines for cervical cancer screening. This article discusses the data and the current guidelines for cervical cancer screening in the immunocompromised population.

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Obstet Gynecol Clin N Am 40 (2013) 339–357
http://dx.doi.org/10.1016/j.ogc.2013.02.005 **obgyn.theclinics.com**

CERVICAL CANCER SCREENING IN WOMEN INFECTED WITH HIV

HIV and Human Papillomavirus Interaction

Human papillomavirus (HPV), a nonenveloped DNA virus, has been identified as the cause of anogenital cancers. In the 1990s, a subset of HPV was identified as a necessary, but not sufficient, cause of cervical cancer. This subset was called oncogenic HPV or high-risk HPV (hrHPV) and included HPV subtypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.[3] In the immunocompetent host, it is estimated that hrHPV infection causes high-grade precancerous lesions (CIN3) to develop slowly over many years (7–8 years), and causes CIN3 to become invasive cervical cancer (ICC) over an additional 5 to 7 years.[3] However, in HIV-infected women the time to progression to ICC is much shorter. In a cancer–acquired immunodeficiency syndrome (AIDS) registry linkage study from 11 sites in the United States (1995–1998), Frisch and colleagues[4] reported that the mean age difference from in-situ cervical cancer to ICC was 3.2 years for women with an AIDS diagnosis compared with 15.7 years for women in the general population. It has been shown that HIV-infected women have a higher prevalence of non-16 and non-18 hrHPV, a higher risk of multiple HPV infections, a higher persistence of HPV infections, as well as an increased risk of progression to precancerous or cancerous cervical lesions compared with HIV-uninfected women.[5,6] In a meta-analysis of 20 studies published between January 1989 and June 2005, with a total of 5578 HIV-infected women with available baseline cervical Papanicolaou (Pap) test and HPV genotyping throughout the world, the investigators reported a baseline rate of normal cytology in 58%, atypical squamous cell of undetermined significance (ASCUS) or low grade squamous intraepithelial lesion (LSIL) in 37% and high grade squamous intraepithelial lesion (HSIL) in 5% of HIV-infected women (WHIV). In addition, they showed that the rate of HPV prevalence increased with the degree of cytologic abnormality: 36.3% for those with normal cytology, 69.4% for ASCUS/LSIL, and 84.1% for HSIL. Multiple HPV infection prevalence was 11.9% for normal cytology, 34.7% for ASCU/LSIL, and 41.1% for HSIL. Among those with normal cytology at baseline, the prevalence of HPV was 57.4% in South/Central America, 56.6% in Africa, 32.4% in Europe, 31.4% in North America, and 31.1% in Asia. Among those with HSIL, the prevalence of any HPV was similar to that in the general population (84.1% for WHIV compared with 84%). However, the rate of multiple HPV infections was higher for WHIV than in the general population (41.4% vs 6.7%). In addition, there is a lower prevalence of HPV16 among HIV-infected women with HSIL (odds ratio [OR] = 0.6, 95% confidence interval [CI] 0.4–0.7) and a higher prevalence of HPV18, 33, 51, 52, and 58 than in the general population.

Molecular studies have shown that, in the HPV-infected cell, the viral early proteins E6 and E7 interact with intracellular growth–regulating host cell proteins (p53 and retinoblastoma protein), which leads to a disturbance of the regulation of DNA replication, repair, and cellular growth.[7,8] Moreover, in vitro data have shown that the transactivator of transcription (tat) protein may enhance the expression of E6 and E7 proteins,[9] although this has not been shown in in vivo models.

Palefsky[10] proposed a pathogenesis model in WHIV in which, early in the HPV infection, the specific immune response to HPV plays a major role in the control of HPV infection as well as the development of squamous intraepithelial lesions (SILs) or cervical intraepithelial neoplasia (CIN) but, later on, cellular genetic change and chromosomal instability would play a predominant role in the transformation of advanced precancerous lesions to ICC. In this model, as long as the effects of immunosuppression from HIV remained minimal, the HPV infection would be limited with little epithelial