The Impact and Burden of Human Papillomavirus–Associated Disease

Barbara S. Ducatman, MD

Papillomavirus, a ubiquitous double-stranded deoxyribonucleic acid virus, has been identified in almost all mammalian species, and in birds, snakes, and turtles, although the virus is host (species) specific. More than 170 human papillomaviruses (HPVs) have been sequenced. The viral genome is approximately 80 kilobases in length and encodes 6 early proteins needed for viral replication as well as 2 late capsid proteins (L1 and L2). The virus infects the basal layer of mucosal surfaces and skin. HPV genotypes classified as high-risk are associated with cancer at a number of sites. The percentage of cancers associated with HPV infection and its worldwide disease burden is highest for cervical cancer followed by cancers of the anus, vagina, penis, vulva, and oropharynx. However, even those HPV types that are considered low-risk can be associated with other lesions, including but not limited to verruca vulgaris (warts), genital condylomas, and squamous papillomas of the respiratory tract.

The development of a cervical cancer screening test by George Papanicolaou in 1927, named in his honor, and its widespread adoption in the 1940s decreased cervical cancer mortality rates throughout the developed world. Further investigations over the decades led to the identification and classification of precancerous cervical neoplasia with nomenclature changes from mild/moderate/severe dysplasia/carcinoma in situ to cervical intraepithelial neoplasia (I/II/III) and finally to low- and high-grade squamous intraepithelial lesions. At the same time, treatment for precancerous neoplasia has become less invasive (including the loop electrosurgical excision procedure). Increased understanding of the role of HPV in cervical neoplasia and the molecular underpinnings have led to the development of screening tests for high-risk HPV types and vaccinations targeted at the highest-risk types.

Although cervical cancer mortality rates have fallen throughout the developed world, the lack of access to medical care, including screening for cervical cancer, has meant that cervical cancer remains an important cause of morbidity and mortality in developing countries. In the setting of immunosuppression, infection with HPV is associated with increased rates of neoplasia in the setting of human immunodeficiency virus (HIV) and with posttransplant neoplasia. In addition, cervical cancer rates remain high in pockets of the United States and are associated with socioeconomic and racial disparities. One such pocket includes Appalachia, including Kentucky and West Virginia. This association led to this special section in Archives of Pathology & Laboratory Medicine on the impact of HPV-associated disease, with contributions from medical students and pathology faculty, fellows and residents from West Virginia University. This special section includes articles on the role, pathogenesis, and diagnosis of HPV-related disease for all sites.

The paradigm for cervical cancer screening is under review. Pure cytology is no longer an option and the current guidelines incorporate HPV genotyping into the algorithmic approaches. The current debate centers upon whether testing for DNA is by itself sufficient for initial screening in adult women or whether cotesting is a better screening paradigm. Flanagan summarizes the debate based not only on the traditional benefits and harms of screening tests, but also on other considerations such as the effect on the cytotecnology workforce. While primary HPV testing has not been widely adopted in the United States, several European countries are in the process of piloting or adopting this method.

As an increasing number of girls and young women are vaccinated against the highest-risk HPV genotypes, the role of non-16/18 types will become relatively more important. Even though new vaccines contain more types, the initial vaccines contained only types HPV 16 and 18. The importance of non-16/18 HPV types and their association with cervical precancerous lesions and invasive carcinoma, particularly in the setting of coinfection with HIV neoplasia, is discussed by Robadi and colleagues.

Nweke et al discuss the impact of HPV infection in the developing world, with emphasis on sub-Saharan Africa, where cervical cancer is still the most important cause of years of life lost due to cancer in women. This sobering finding demonstrates both the ongoing global burden of HPV-related cancer as well as the impact of screening upon cervical cancer rates. Major challenges to eradicating HPV-related disease in this population include lack of access to medical care, lack of a trained cytotecnologist workforce, and lack of access to vaccinations. In the developing world, primary HPV screening is likely to be adopted as cost and...
ease of use provide more access to this technology than traditional cytology.

Bacaj and Burch discuss various manifestations of HPV infection in the skin. In this setting, HPV lesions can vary from common warts of the soles and palms to invasive cancers of the anogenital region, many with specific associations to HPV types. In addition, the body site and host factor may also play a role in the process. Similarly, Hanbazazh and Gyure discuss ocular disease associated with HPV infection. In this setting, HPV is implicated in the pathogenesis of squamous papillomas, pterygia, and ocular surface squamous neoplasia.

The development of HPV-related neoplasms is especially important in the development of neoplasms associated with immunosuppression. Stiebing and colleagues discuss the pathogenesis of HPV-related neoplasms in the setting of solid organ transplants. Since transplant recipients are generally older, they are less likely to have been vaccinated against HPV. As the number and type of these transplants increase, the number of patients at risk will likewise increase.

Ducatman describes the role of HPV in oropharyngeal squamous cell carcinomas. This association is recent, but the incidence of such tumors is increasing. It is important that pathologists recognize these tumors and that they be appropriately tested for HPV as this will change staging, management, and prognosis. In addition, implications for prevention strategies for HPV-positive oropharyngeal carcinoma are still under consideration with many challenges. In view of this association, Kunkle and Rosado describe a promising new frontier in HPV management and review the role and implications for therapy of the programmed death receptor-1 (PD-1)/programmed death ligand-1 (PD-L1) in this setting.

Within the last century, the incidence and mortality of cervical carcinoma have dropped dramatically throughout the developed world owing to screening and treatment of precancerous lesions. Concomitantly, research has identified the role and pathogenesis of HPV infection in cervical cancer and other neoplasms, with the development of vaccines effective against the highest-risk types. Unfortunately, these advances are not uniform throughout the world or even the United States. Hopefully, better access to medical care and vaccination strategies to immunize both boys and girls throughout the world with more inclusive vaccines will eradicate the scourge of HPV-related neoplasia in the 21st century.