

## Vaccination as a Tool for Cancer Prevention

Infectious agents, such as viruses and bacteria, are the causes of several common cancers. Infection with the bacterium *Helicobacter pylori* predisposes to gastric cancer. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are associated with liver cancer, and Epstein-Barr virus (EBV) is associated with lymphoma and nasopharyngeal cancer. Human papillomavirus (HPV) is a major cause of cervical, anal, penile, and oropharyngeal cancer. Together, infection-associated tumors make up nearly 20% of all cases of cancer worldwide, causing more than 2 million malignancies per year. Most of these cases occur in developing countries. Under normal circumstances, immune surveillance helps to keep many of these virus-associated cancers in check, but in immunocompromised persons, such as those with late-stage HIV infection, the incidence and aggressiveness of these cancers increase. HBV and HPV vaccines are effective and in use, and vaccines against other cancer-causing agents are in development. Because many virus-associated cancers occur in the developing world (such as EBV-associated Burkitt's lymphoma in Africa and HBV-associated hepatocellular carcinoma HCC in Asia), the development and deployment of vaccines to prevent infection with HPV, HBV, HCV, and EBV can serve as effective preventative tools to reduce the burden of cancer morbidity and mortality worldwide.

### Introduction: Cancer-Causing Infections

In the developing world, cancer is estimated to afflict 10 million people per year. Worldwide efforts to prevent cancer have generally focused on behavioral changes, such as smoking cessation. Because infectious agents cause some of the more common human cancers, understanding the role of the immune system is necessary to maximize cancer prevention strategies. The immune system has an endogenous role in preventing some cancers and can be stimulated with vaccines to prevent infection with cancer-causing viruses.

One of the paradoxes of cancer biology is that a lack of immune surveillance (such as in HIV-infected individuals or immunosuppressed organ transplant recipients) can lead to cancer, and chronic inflammation due to persistent infection can also do so. Chronic inflammation as a result of HBV or HCV infection leads to HCC, usually after the patient progresses to cirrhosis. In gastric cancer, nearly 60% of all cases in developed countries and 75% of cases in developing countries are attributable to chronic infection with *H pylori*.<sup>1</sup> It is likely that chronic inflammation due to *H pylori* leads to intestinal metaplasia of the gastric epithelium and eventually to gastric cancer.<sup>2</sup> Long-term infection with HPV and EBV leads to transfer of oncogenes present in the viral genome to human cells, thereby promoting cancer development.

Harnessing the immune system to prevent or clear cancer is a major goal of cancer research. Vaccination campaigns have been enormously successful in reducing the global burden of infectious diseases. A worldwide infrastructure exists for the manufacture, distribution, and administration of vaccines in urban, suburban, and rural areas. The use of vaccines to prevent cancer caused by chronic infection with oncogenic agents has had a substantial benefit in the developed world and could have a major effect on cancer incidence in the developing world. This article will review the most common infection-related cancers and the role of vaccines for cancer prevention worldwide.

### HPV and Cancers of the Anogenital Tract and Oropharynx

HPVs are commonly spread through sexual contact. These viruses are the cause of genital warts, and subtypes 16, 18, 31, 33, and 35 are the major subtypes that cause cervical, anal, and head and neck cancer.<sup>3</sup> HPV infection is associated with 100% of cases of cervical cancer. The incidence of infection with HPV is far higher than the incidence of cancer, because the immune system clears most infections.<sup>4</sup> Routine Papanicolaou smears can monitor for early signs of cervical cancer, but many at-risk women in the United States and elsewhere do not receive appropriate gynecologic care.<sup>5</sup>

During the past 30 years, the incidence of aggressive serotype HPV-associated squamous-cell carcinoma of the anus has increased. This increase largely began in men who have sex with men, but increases in women have also been observed.<sup>3</sup> HPV is also associated with cancer of the vagina, vulva, and penis, although these are much less common than cervical cancer.

Squamous-cell carcinoma of the oropharynx and head and neck is associated with tobacco and alcohol use, but HPV serotypes 16 and 18 are commonly observed in a subset of persons with this cancer.<sup>3</sup> Of interest, the percentage of HPV-positive oral cancers is reported to be increasing in several countries.<sup>6</sup> This increase is attributed to changing sexual practices, suggesting that HPV-associated oral cancer, like HPV-associated anal and cervical cancer, can be considered a sexually transmitted infection.<sup>6</sup>

### Hepatitis B and C Viruses and HCC

Chronic HBV infection is highly prevalent throughout the developing world, particularly in Asia and Africa, where some countries have a prevalence rate as high as 12% of the total population. It is estimated to cause more than 1 million annual deaths worldwide, with one third of these deaths caused

by HCC and the remainder by cirrhosis. 1 Chronic HBV infection confers a 20 times increased risk for HCC. HBV vaccination is now included in the standard childhood vaccination series in the United States, but immigrant and older populations can have high HBV carrier rates. 7 Intrapartum transmission is a major cause of transmission of HBV to children. To prevent HBV infection, hepatitis B immune globulin, along with hepatitis B vaccine, must be given to neonates of HBV-positive mothers (see "Key Recommendations for Healthcare Providers to Prevent Cancers Caused by Infectious Disease").

HCV infection is another a major cause of HCC. Whereas the carrier rate of HCV in the United States was estimated at 1.6% in 2002, in Africa the prevalence ranged from more than 8% in Northern Africa to less than 2% in Southern Africa. 1 Vaccines for HCV are in development, but for patients who have already contracted HCV, a regimen involving 6 months of pegylated interferon alpha and ribavirin can lead to eradication in up 60% to 80% of patients. 8 Active surveillance for HCV and aggressive attempts at eradication can therefore reduce the subsequent risk for cancer in populations at risk.

### **EBV-Associated Cancers**

EBV is the primary cause of infectious mononucleosis, a typically benign disease of adolescence and young adulthood. However, the virus is also a causative agent in many aggressive neoplasms, including 20% of cases of Hodgkin's lymphoma (one of the most common lymphomas of adolescence), nasopharyngeal carcinoma, and a subtype of Burkitt's lymphoma. 1 Nasopharyngeal cancer affects approximately 80,000 people each year, predominantly in less developed countries. Most of these cases are attributable to EBV infection. 1 Although this cancer is curable with intensive chemotherapy and radiation therapy, most of the people affected by this cancer do not have access to these treatments.

Like nasopharyngeal cancer, Hodgkin's lymphoma is highly treatable. More than half of Hodgkin's lymphoma cases occur in less developed countries, however, and curative treatment is often not available. The iconic image of a sub-Saharan African child with a very large facial or neck mass is an easily recognizable sign of endemic Burkitt's lymphoma caused by EBV infection. As many as 6800 cases of Burkitt's lymphoma caused by EBV occur every year, with more than 90% of these infections occurring in less developed countries. 1 EBV-associated non-Hodgkin's lymphoma is particularly common in patients with advanced HIV infection. An estimated 68,000 cases of EBV-associated non-Hodgkin's lymphoma occur annually, and two thirds occur in developing countries. 1

The causative infectious agent for peptic ulcer disease, *H pylori*, is also a known cancer-causing agent. Chronic infection with this pathogen predisposes to stomach cancer and to gut mucosa-associated lymphoid tissue (MALT) lymphoma. 4 *H pylori* (other risk factors include diet and excessive alcohol intake). In 2002, it was estimated that *H pylori* caused as many as 600,000 cases of gastric cancer per year worldwide. 1 Eradication of *H pylori* can be accomplished with antibiotic therapy; however, the very high burden of infection in many countries (for example, in sub-Saharan Africa, more than 75% of adults are infected with *H pylori*) and the relative ease of reinfection make treatment of asymptomatic carriers unfeasible. 2 Because the infection first occurs in young children, *H pylori* seems to be an amenable target for vaccine development to prevent colonization and subsequent stomach cancer and gut-associated MALT lymphoma. Until a vaccine becomes available, healthcare providers should screen for dyspepsia and peptic ulcer disease and offer *H pylori* testing to affected patients. Healthcare providers should administer drug therapy for eradication of *H pylori* in those who are symptomatic and *H pylori* -positive.

### **Human Herpesvirus 8: Kaposi's Sarcoma**

Human herpesvirus 8 (HHV-8) is the causative agent of Kaposi's sarcoma, a once-rare sarcoma of blood vessels. Before the AIDS epidemic, Kaposi's sarcoma was primarily known to affect Mediterranean or eastern European men or immunosuppressed patients, such as organ transplant recipients. 9 With the increasing worldwide prevalence of HIV infection, most cases of Kaposi's sarcoma are now associated with HIV or AIDS. In 2002, it was estimated that more than 60,000 cases of Kaposi's sarcoma occur yearly, 1 and it is the most common type of cancer reported in some African countries highly affected by HIV, such as Zimbabwe. The best treatment for Kaposi's sarcoma in HIV-infected patients is initiation of antiretroviral agents to reduce HIV viral load and allow restoration of immune system function. Sometimes this is sufficient to cause regression of the cancer. In other cases, the cancer continues to spread and combination chemotherapy is required. 9

### **Role of Vaccines for Cancer Prevention in the United States**

**HBV vaccine.** In 1991, the Centers for Disease Control and Prevention (CDC) recommended adoption of a comprehensive strategy for prevention of HBV infection, which included:

Routine maternal prenatal testing for HBV;

Immediate postpartum intervention to prevent maternal to child transmission;

Universal vaccination of children for HBV;

Vaccination of all adolescents who had not received HBV vaccine previously; and

Vaccination of adults at risk for becoming infected with HBV. 10

The childhood immunization schedule, a 3-vaccine series administered in the first year of life, confers long-term immunity to HBV. Infants born to HBV-positive mothers must receive both vaccination and hepatitis B immune globulin within the first 12 hours of life. This regimen is 85-95% effective in preventing transmission of HBV. Because children are at increased risk for becoming chronic carriers when infected with HBV, starting the vaccine at birth and completing the series during routine well-child visits during the first year of life decreases the risk for infection from HBV-positive household contacts. Analysis of immunization rates in newborns in the United States from 2003-2005 showed only a 50% vaccination rate, leaving many infants unprotected from HBV infection. Clearly, the United States needs to increase newborn vaccination rates for HBV. 11

**HPV vaccine.** Two HPV vaccines are approved for use in the United States: Gardasil Both vaccines are equally effective at preventing HPV infection caused by the serotypes contained in the vaccines, and both will prevent development of high-grade cervical lesions caused by the corresponding serotypes. These vaccines are most effective when given to women and girls who have not been exposed to HPV. 12 However, in a mixed population of HPV-exposed and HPV-unexposed young women, compared with placebo, vaccination with Gardasil A corresponding reduction in the number of women who required invasive surgical resection of their precancerous lesions suggests that even in older, HPV-exposed women, vaccination may be helpful in reducing cervical cancer rates. 13 The follow-up timeframe for these vaccines is still short, so it is not clear how long the protective effect will last. 12 Additional postapproval studies are ongoing to determine the duration of protection and to determine whether post exposure vaccination is warranted.

The availability of HPV vaccines against serotypes 16 and 18 gives healthcare providers the tools to prevent HPV infection and subsequent cervical cancer. The US Food and Drug Administration (FDA) approved Gardasil These vaccines may also be effective in preventing cancer of the oropharynx and anus caused by HPV 16 and 18 in both men and women. 6,15

Whereas HPV vaccines have been approved and are being administered in the United States, the uptake of the vaccines has been uneven. A backlash against HPV vaccination has occurred in some communities. Further interventions are required to improve vaccination among those most at risk for invasive cervical neoplasia. 5 Clinicians should offer HPV vaccination to all adolescent girls and young women who have not yet had their sexual debut, and they should consider giving the vaccine to young women after sexual debut, on the basis of the findings described above. These vaccines do not cover all of the subtypes of HPV that cause cervical cancer, and widespread vaccination does not replace the need for intermittent cervical cancer screening, although it is projected to reduce the number of invasive procedures. 12

### **Cancer Prevention Outside of the United States**

**Role of vaccines.** The use of vaccines and eradication treatments to prevent infection-caused cancer in the United States and other developed countries will continue to reduce mortality and morbidity from these diseases. However, the major burden of disease and corresponding mortality lie in the developing world. 4 Taken together, the number of infection-related cancers is estimated at nearly 2 million cases per year, accounting for almost 20% of all cancer cases. 1 Widespread application of vaccines for HBV and HPV could decrease the global burden of cancer by 900,000 cases per year, on the basis of 2002 estimates. 1

The HPV vaccine is approved for use in more than 60 countries. Widespread vaccination for HPV coupled with limited cervical cancer screening can be considered cost-effective in developing countries if a vaccine can be delivered for approximately \$1 per dose (in a 3-dose regimen). 16 The current course in the United States costs more than \$300 USD. Improvements in HPV vaccines to make them more thermostable and efficacious, and less costly, will increase the feasibility of vaccinating adolescents in developing countries. 4

Drug treatment of HCV and H pylori infections to prevent cancer. Development of new vaccines or widespread identification and eradication efforts could further reduce the global cancer burden by reducing the carriage rate of H pylori Eradication of HCV by use of ribavirin plus pegylated interferon, although expensive, could eliminate the nearly 200,000 cases per year of HCC that are attributed to HCV. 1 To eliminate HCV in less developed countries successfully and cost-effectively, either a vaccine against HCV or a less burdensome eradication regimen is needed.

**Burden of HIV as a cancer predisposition syndrome.** The growing HIV epidemic is adding to the already substantial burden of cancer in lower-income countries (and in affected populations in the United States). Chronic HIV infection should be considered a cancer predisposition syndrome. Loss of immune surveillance as a result of HIV infection can lead, in HPV infection, to a rapid progression of precancerous lesions to cancer, and to increases in de novo cancer, particularly in HHV-8 and EBV-infected individuals. 1,17 Restoration of immune function as evidenced by normalizing CD4 helper T-cell numbers after initiation of highly active antiretroviral therapy (HAART) can lead to stabilization or regression of cancer. However, in lower-income countries, initiation of HAART continues to encounter multiple barriers (lack of healthcare providers, lack of drug distribution infrastructure, and cultural barriers to testing and starting treatment). 18 Although initial trials of an HIV-prevention vaccine have not succeeded, additional trials of new strategies for an HIV vaccine are ongoing and under development.

**Role of vaccines in immunocompromised hosts.** For patients who are already HIV-infected, the ability to respond to an antiviral vaccine, such as the HBV vaccine, may be severely attenuated, depending on their CD4 count. 19 Vaccination before HIV infection (such as in an HIV-negative child) may prevent subsequent infection with the target of the vaccine, even if the patient has become HIV-positive. Much depends on the degree of destruction of the immune system and the extent to which the immune system is reconstituted after starting antiretroviral therapy.

### Future Directions

The current availability of vaccines against HPV and HBV cancer-causing viruses could prevent nearly 1,000,000 annual cases of cancer throughout the world. 1 Barriers to widespread vaccination include expense, lack of sufficient healthcare personnel, problems with drug delivery and storage, and opposition of the local population. HPV and EBV vaccines are being deployed and improved, and an effort to develop vaccines against HCV and EBV continues. These new vaccines, along with those currently in use, have the promise of substantially reducing global morbidity and mortality from cancer. 4 Finally, advances in immunobiology will further our understanding of the pathogenesis of cancer and may enable the development of vaccines to prevent other cancers not caused by infectious agents. 20

### About the Author

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