



Viruses and Cancer

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Introduction

Over the last few decades, epidemiologic studies have provided clues linking infectious agents, particularly viruses, to some types of cancers. It is estimated that 15-20% of human malignancies have an infectious etiology with viruses accounting for approximately 10-15% of cases worldwide¹⁻³. Some of the viruses and the malignancies associated with them include: human papillomavirus (HPV) and cervical and other anogenital cancers; hepatitis B and C viruses (HBV, HCV) and hepatocellular carcinoma (HCC); Epstein-Barr virus (EBV) and nasopharyngeal carcinoma (NPC), Burkitt's lymphoma (BL), and Hodgkin's disease; human T-cell lymphotropic virus type-1 (HTLV-1) and adult T-cell leukemia and lymphoma (ATLL); human immunodeficiency virus type-1 (HIV-1) and lymphoma; and human herpesvirus type-8 (HHV-8) and Kaposi's sarcoma (KS). This review will attempt to summarize the current level of knowledge with respect to viruses, cofactors, and the spectrum of malignancies caused by or associated with them.

Human papillomavirus

HPV is one of the most common sexually transmitted infections worldwide and the major cause of cervical cancer⁴. The molecular detection of the virus in cervical lesions prompted the hypothesis and subsequent studies demonstrating the association of HPV with penile cancers as well as anal cancers in both males and females⁵. HPV is transmitted through sexual intercourse with an infected partner with the risk of infection proportional to number of sexual partners and encounters^{6,7}. Cervical carcinoma is the second leading cancer among women worldwide⁸. In Hawaii, as in the rest of the United States, the overall incidence of cervical cancer has decreased over the past 30 years due largely to the widespread use of Papanicolaou screening. These early screening programs have led to detection of cervical precancerous lesions with subsequent increase in appropriate medical interventions or follow-up. However, the morbidity and mortality from cervical cancer continues to be a major health issue among women in resource-limited areas such as Africa.

Of the approximately 100 different genotypes of HPV, approximately 30 infect the genitals and at least 10 of these are considered to be oncogenic or potentially oncogenic, including HPV 16 and 18, the types most frequently found in cervical cancers⁹.

Hepatitis B and C

Both HBV and HCV viruses are major causes of HCC, which account for over 80% of primary liver cancers worldwide^{10,11}. Worldwide, HCC ranks as the fourth most common cancer and the third most frequent cause of cancer death¹². The incidence of HCC varies geographically with higher rates in sub-Saharan Africa, China, and southeast Asia where liver cancers are primarily caused by HBV¹³. In the United States, as well as Japan and Europe, HCC rates are much lower and are predominantly caused by HCV¹³. Although relatively rare in North America, the rates of HCC in the United States have increased 70% with the rates in men being 2 to 4 times higher than in women¹². In Hawaii, the incidence of HCC is higher compared to the rest of the U.S. and this differential is more apparent in men than in women (Figure 1). This is likely due to the high proportion of individuals immigrating from high-incidence areas.

HBV is transmitted through infected blood or blood products via contaminated needles or blood transfusions. HBV can also be acquired sexually through exposure to infected body fluids. HCV is primarily transmitted through contaminated needles or blood transfusions. In the U.S., before widespread screening of blood products was initiated, HCV was primarily transmitted by transfusion of contaminated blood products¹⁴. Today in the U.S., it is usually acquired via needle sharing with intravenous drugs¹⁴.

Epstein-Barr virus

EBV is a ubiquitous infection worldwide transmitted orally through saliva and breast milk. EBV is associated with undifferentiated nasopharyngeal carcinoma¹⁵, BL¹⁶, Hodgkin's disease¹⁷, and other lymphoid malignancies.

NPC incidence has a wide geographic and ethnic variation. Nasopharyngeal carcinoma is common in southern China and among Chinese in Singapore and Hong Kong, as well as in parts of southeast Asia, where men are most affected¹⁸. In Hawaii, rates of NPC are higher among Chinese than other ethnic groups. BL is endemic in tropical areas of Africa and generally rare in other parts of the world. This childhood cancer is characterized by tumors involving the jaws, maxillaries, and/or abdomen¹⁶. Approximately a third of Hodgkin's disease cases have EBV or EBV gene products detected in Reed-Sternberg cells¹⁷. The incidence of Hodgkin's disease peaks

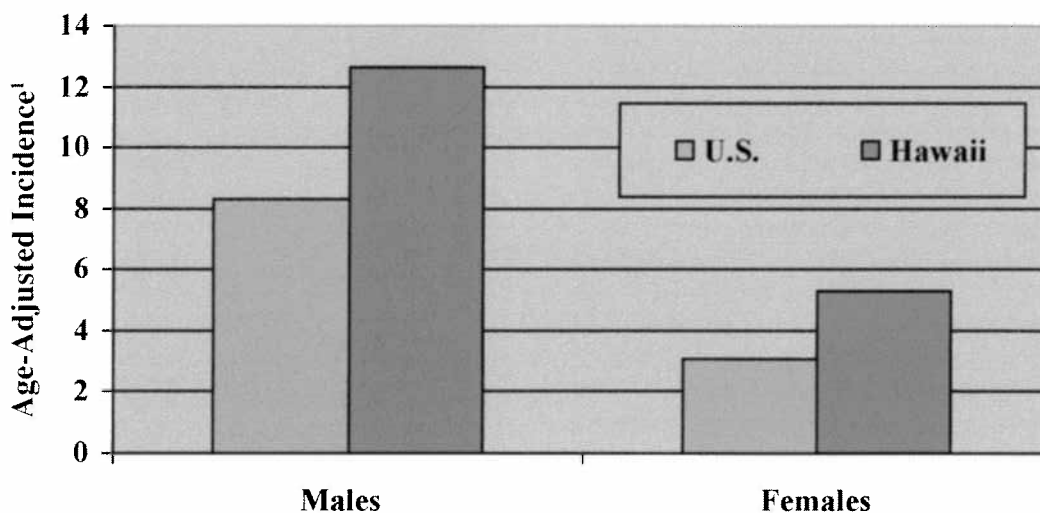


Figure 1.— Hepatocellular Cancer in Hawaii and U.S. 1997-2001

¹ Incidence rates are per 100,000 and are age adjusted to the 2000 U.S. standard population.

Source: Hawaii Tumor Registry, Cancer Research Center of Hawaii; Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute

in young adults followed by a second larger peak in elderly adults¹⁹. This age pattern may reflect different age-related responses to EBV-infection.

Human T-cell lymphotropic virus type 1

The retrovirus, HTLV-1, is the cause of ATLL²⁰. HTLV-1 is transmitted through breastfeeding, sexual intercourse, intravenous drug use, and blood transfusions. HTLV-1 prevalence exhibits geographic and ethnic variation. At least 10% of the adult population is infected in endemic areas such southern Japan, sub-Saharan Africa, the Caribbean, parts of South America, Papua New Guinea, and some areas of the Middle East²¹. In Japan and other endemic areas, the risk of ATLL increases dramatically between ages 40 and 65 after which risk declines steadily²².

Human immunodeficiency virus type-1

Shortly after the HIV-1 epidemic was recognized, malignancies were shown to be associated with the virus, either directly or indirectly through the immune dysfunction caused by HIV-1^{23,24}. Although a direct cause and effect has yet to link HIV-1 to malignancies, its impact on the immune regulatory system likely plays a role in B-cell lymphomas and HIV-1-associated cancers^{25,26}.

Human herpesvirus type-8

HHV-8, also known as Kaposi's sarcoma herpesvirus (KSHV), may be causally related to KS, primary effusion lymphoma and multicentric Castleman's disease^{27,28}. While initially linked only to HIV-1-associated KS, other epidemiological forms of KS as well as other lymphoid malignancies have now been tied to HHV-8/KSHV.

Mechanisms and Epidemiology of Viral Oncogenesis

Viruses that are associated with cancers have important similarities and differences, particularly with respect to mechanisms of oncogenesis^{1,3}. HPV is a small DNA virus, which causes malignant trans-

formation though inactivation of human tumor suppressor proteins, p53 and retinoblastoma, by viral proteins, resulting in dysregulation of cell growth mechanisms and genetic instability. HPV is able to integrate into the host's DNA and thus contribute to cervical carcinoma⁴. HBV and HCV cause malignancy through indirect means. Chronic HBV and HCV liver infections result in inflammation, cell death, tissue scarring, and, finally, clonal regeneration of tissue. This cycle disrupts normal cell growth and increases the risk of malignant transformation¹¹. HBV, a partially double-stranded DNA virus, is phylogenetically unrelated to HCV, an RNA virus. HBV uses an RNA intermediate for its replication and, like HPV, is able to integrate into the host genome, which may contribute directly to carcinogenesis²⁹. As an RNA virus, HCV is unable to integrate into genomic DNA and it is not completely clear how the virus establishes a chronic infection. EBV, a large, double-stranded DNA virus, integrates into the host genome during the lytic phase of infection. Following primary infection, EBV establishes latent infection in B cells establishing a lifelong reservoir for the virus¹⁸. Latently infected cells can subsequently undergo uncontrolled proliferation leading to malignant transformation.

Presence of oncogenic viruses is common in the general population but only a limited proportion of infected individuals develop malignancies. For example, HPV is prevalent in approximately 25% of all sexually active women but most HPV-infected women remain asymptomatic and relatively few progress into cervical cancer⁴. In areas of highest HBV prevalence (China and Africa), up to 15% of the population are chronic HBV carriers, but only 25% of those infected develop HCC³⁰. In the U.S. where HCV-associated HCC is the predominant type, overall prevalence of HCV is less than 2%³¹. After initial infection, approximately 80% of individuals develop chronic HCV infection and, of these carriers, 1-5% progress to HCC 20-30 years later³². EBV is a ubiquitous infection with 80% of individuals worldwide infected by the age of 30¹⁶. Despite its high prevalence, with the exception of endemic areas of tropical Africa, EBV-associated BL is relatively rare¹⁶.

The incongruent rates of infection and malignancies underscore the potential role of cofactors in virus-associated cancers. For cervical cancers, co-factors such as parity, smoking, and concurrent infection with other sexually transmitted pathogens may play a role³¹. Risk of HBV and HCV-associated HCC may be influenced by cofactors such as liver cirrhosis, alcohol consumption, cigarette smoking, and for, HBV, exposure to aflatoxin fungus-contaminated food products^{12, 13}. NPC is strongly associated with the consumption of salted fish, possibly due to high nitrosamine content; as well as a potential genetic predisposition¹⁸. Innate immune responses to EBV may also influence NPC development with individuals developing IgA antibodies to EBV having an increased risk for NPC¹⁸. In tropical Africa, development of endemic BL may be exacerbated by chronic infection with *Plasmodium falciparum*, (malaria), which suppresses cell-mediated immunity and consequently increases risk of BL³³. BL also involves the activation of the c-myc oncogene resulting from a specific chromosomal translocation³³. In addition to its role as a cancer-associated virus, HIV-1 may also be considered a cofactor³³. EBV and HHV-8/KSHV may increase their risk in causing lymphoma and KS, respectively, in HIV-1-infected individuals.

Cancer-associated viruses commonly have the ability to develop persistent or chronic infections. It is this chronicity that permits malignant progression as most cancers take decades to develop. For some oncogenic viruses, the age of infection is critical to the establishment of chronic infection and subsequent malignant progression. Infection with EBV during infancy and very early childhood increases the risk of BL¹⁶. This is consistent with the high rates of BL in areas of tropical sub-Saharan African where primary EBV infections usually occur before age 2. Infection with EBV during later childhood increases the risk of NPC¹⁸. High rates of NPC are observed in southern China and parts of southeast Asia where primary infection occurs among school-aged children primarily through young household or community contacts¹⁸. Very early infection with HBV increases the risk of HCC, particularly among infants from HBV-infected mothers who are HBV e antigen-positive carriers or horizontal transmission from recently infected young household members or playmates³⁴. Nearly all HBV-infections acquired at an early age become chronic and are likely to progress to HCC. In contrast, HBV acquired during adulthood rarely becomes chronic and, consequently, rarely progresses into HCC³⁴. Most HPV infections are transient, particularly in young women, and resolve within a few months⁵. However, a small number of HPV-infected women develop persistent infections and it is these women who are at greatest risk for developing cervical cancer³⁵.

Future Directions

As in other infectious-related diseases, the impact of vaccines has or could dramatically influence the incidence of virus-associated malignancies. For instance, HBV vaccine, effective against all HBV genotypes, could substantially reduce the rate of HCC worldwide. A vaccine against HCV could potentially have the same effect, as could other measures such screening blood products. Recent development of a prophylactic HPV vaccine, which has shown great promise in early trials, has the potential to offer primary prevention of HPV infection with subsequent reductions in cervical cancer. Unfortunately, no HTLV-1 or HIV-1 vaccine is available yet. Primary prevention of HTLV-1 and HIV-1 has been addressed through education,

decrease risk of exposure, and screening of blood products. Future successes in preventing virus-associated malignancies will likely benefit from further advances in preventative measures, including vaccine development, appropriate screening, and elimination of acute or chronic infection.

For more information about the Cancer Research Center of Hawaii, please visit our website at www.crch.org.

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