

Human Cancer Viruses: Past, Present and Future

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Viruses	Associated cancer types	Time of discovery	Mode of transformation	Mechanism
Human papilloma virus (HPV)	cancers of the cervix, anus, vulva, vagina, penis, and oropharynx.	1984-1986	direct	production of 2 viral oncoproteins E6 and E7
Epstein-Barr virus (EBV)	Burkitt's lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma and non-Hodgkin lymphoma associated with post-transplant or HIV immunosuppression	1964	direct	production of viral oncoproteins during lytic infection
Kaposi's sarcoma virus (KSHV)	Kaposi's sarcoma, primary effusion lymphoma (PEL), and multicentric Castlemann's Disease (MCD)	1994	direct	production of viral oncoproteins during lytic infection
Hepatitis B virus (HBV)	Hepatocellular carcinoma	mid-1960s	indirect	chronic inflammation
Merkel Cell virus (MCV)	Merkel cell carcinoma	2008	direct	viral genes large and small T (tumor) antigens
Hepatitis C virus (HCV)	Hepatocellular carcinoma	1987	indirect	chronic inflammation
Human T-cell Leukemia virus type 1 (HTLV-1)	Adult T-cell Leukemia/Lymphoma (ATLL)	1980-1981	direct	viral oncoprotein Tax
Human immunodeficiency virus (HIV)	Kaposi's sarcoma	1981	indirect	immunosuppression

Table 1. Human viruses associated with cancers.

In 2008, cancer caused 7.6 million deaths worldwide. Several factors increase the risk of developing cancers such as smoking for lung cancer or sun exposure for melanoma. Infection by viruses is the second leading cause of cancers. It has been estimated that approximately 12% of all cancers world-wide are attributable to viral infections [1]. Cancer causing viruses are termed oncoviruses, and it is of interest to learn more about them.

DNA and RNA oncoviruses

Oncoviruses can be DNA or RNA viruses (Table 1). To date, the DNA viruses which have been implicated in the etiology of human

cancers include human papilloma viruses (HPVs), Epstein-Barr virus (EBV), Kaposi's sarcoma-associated herpesvirus (KSHV), hepatitis B virus (HBV) and the Merkel cell polyomavirus (MCV). Among the RNA viruses, hepatitis C virus (HCV) and the human T-cell leukemia virus type 1 (HTLV-1)-retrovirus are associated with human malignancies [2]. Infection with another retrovirus, human immunodeficiency virus (HIV), although associated with an excess of cancer incidence, is probably not carcinogenic *per se*, but acts mainly *via* immunodeficiency [3]. Except for MCV which remains under further study, all these mentioned viruses have been classified as group 1 carcinogens by the International Agency for Research in Cancer (IARC) [4].

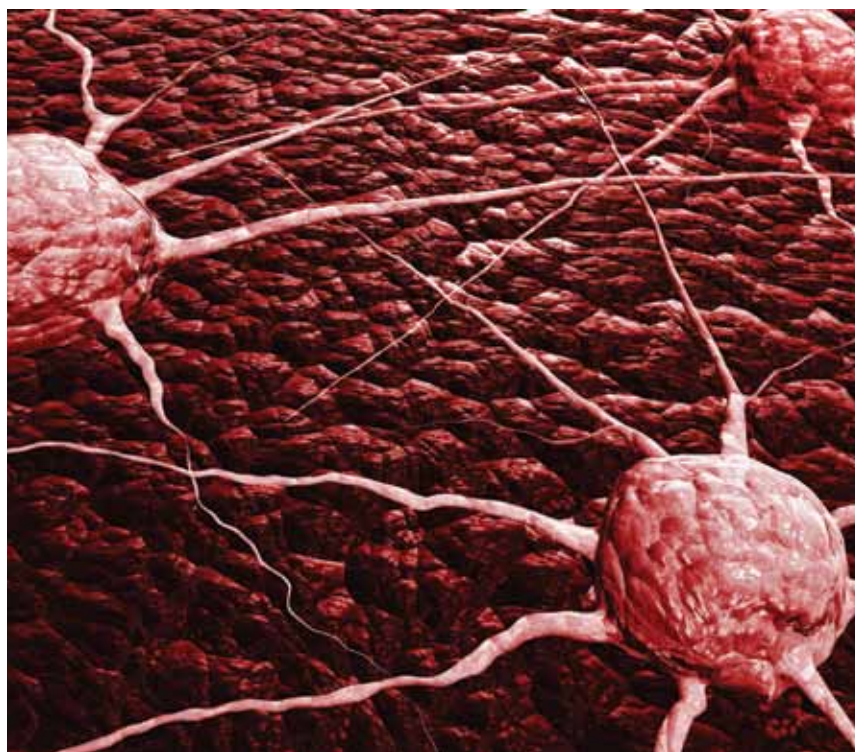
IARC considers that there is convincing evidence that infection with HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 or 66 leads to cervical cancer [5]. These HPV types can be sexually transmitted. HPV 16 and HPV 18 are the most pathogenic and account for approximately 70% of cervical cancers [3], which are diagnosed yearly in nearly 0.5 million women worldwide claiming 0.25 million lives. Evidence supports a contributory roles for HPV 16 and 18 in cancers of the vulva, vagina, penis, anus, oral cavity, oropharynx, larynx, and periungual skin. Collectively, all HPV infections account for approximately 5% of total cancers globally [5].

Epstein-Barr virus (EBV or HHV-4), initially identified in 1964, was the first herpesvirus shown to be oncogenic in humans

[1]. Establishing a direct, indirect or cofactor etiologic relationship between EBV and cancers is more difficult than HPV because of the ubiquitous presence of EBV in the general population [3]. EBV is associated with four types of cancers: Burkitt's lymphoma (one of the most dreaded diseases in sub-Saharan Africa), Hodgkin's lymphoma, nasopharyngeal carcinoma (the most common tumor of males in southern China), and non-Hodgkin lymphoma associated with post-transplant or HIV immunosuppression [3, 6, 7].

Unlike EBV, KSHV, also called human herpesvirus 8 (HHV-8), is not ubiquitous, only 5% of the general population are infected with this virus. In the early 1990s, the increased incidence of Kaposi's Sarcoma (KS) was one of the first obvious manifestations of the acquired immunodeficiency syndrome (AIDS) epidemic. The KSHV virus was subsequently identified and isolated from a case of AIDS-associated KS in 1994. This virus is most probably transmitted *via* oral exchange of infected saliva; it is rarely detected in semen. Both sexual and non-sexual transmissions are possible. Diseases associated with KSHV include Kaposi's sarcoma (the most common malignancy affecting individuals with HIV/AIDS), primary effusion lymphoma (PEL), and multicentric Castleman's Disease (MCD) which, although not formally a malignancy, can evolve into one [7].

HBV is a small DNA virus that can be transmitted from human to human vertically, through close personal contact, through contaminated blood and blood products, or sexually. An effective HBV-vaccine has been available for the last twenty years; however, approximately 360 million people worldwide are still chronic carriers. HCV is a single-stranded RNA virus that is transmitted mostly from unscreened blood transfusions or invasive medical procedures using contaminated equipment. The World Health Organization estimates that 170 million people are infected worldwide, but this number is apparently increasing. Liver cancer or hepatocellular carcinoma is the sixth most common cancer in the world; but ranks third in terms of mortality, due to its very poor prognosis. It is estimated that 54% and 31% of the world total liver cancer cases are attributable to HBV and HCV infection, respectively [3]. The development



of hepatocellular carcinoma is slow generally occurring more than 30 years after infection with HBV or HCV [8].

In 2008, Feng *et al.* [9] discovered MCV, a previously unknown polyomavirus in 80% of Merkel cell carcinoma (MCC) (a rare but highly aggressive neuroendocrine skin malignancy that affects elderly and immunosuppressed patients). MCV was demonstrated to be monoclonally integrated into the host genome in MCC, suggesting that viral infection precedes clonal expansion of the tumor. Because viral genome integration is one of the typical features of virus-mediated oncogenesis, MCV is thought not to be a passenger virus but to play a causative role in tumorigenesis [10].

HTLV-1 was the first identified human retrovirus isolated in 1980 and 1981 from American and Japanese patients suffering from adult T-cell leukemia (ATL), a rapidly fatal disease. Since then, a causal association between the virus and the malignancy has been firmly established. Viral transmission mostly occurs from mother to child through breast-feeding, sexually through partners, or iatrogenically *via* transfusion of infected blood products. HTLV-1 infection is endemic to certain regions, including Southern Japan,

the Caribbean basin, Central and South America, and Central Africa. It is estimated that 15-20 million people worldwide are chronic HTLV-1 carriers of whom 1-5% have lifetime risk of developing ATL [1].

Viral causality of human cancers

The relationship between viruses and cancers has long intrigued researchers. The acceptance of a **virus-cancer association** was initially difficult because viruses were perceived as infectious and transmissible whereas cancers were not. Traditionally, the application of Koch's postulates for disease etiology requires the demonstration that a specific microbiologic agent is responsible for an infectious disease. Koch's postulates are, however, difficult to apply to viral diseases. Asymptomatic virus infection and carriage are the norm for most tumor viruses which complicates Koch's third principle that the cultured microorganism should cause disease when introduced into a healthy organism. It is therefore necessary to develop different criteria for the viral etiology of human cancers. A major complication resides with

the reality that some viruses cause tumors directly while other viruses contribute to tumorigenesis only indirectly.

If the virus has a direct role in cellular transformation, the following criteria can be applied:

- 1) the consistent presence of the viral DNA in tumor biopsies and the persistence of this DNA in cell lines derived from these tumors;
- 2) the demonstration of growth-promoting activity of specific viral genes or of virus-modified host cell genes in tissue culture or animal models;
- 3) the demonstration that the malignant phenotype depends on the continuous expression of viral oncogenes or on the modification of host cell genes containing viral sequences;
- 4) epidemiological evidence that the respective virus infection represents a major risk factor for cancer development [2].

If the virus acts indirectly for tumorigenesis, it is more difficult to define stringent criteria. Indeed, rather than inserting viral oncogenic genes into the host cell or modulating existing cellular oncogenic genes (proto-oncogenes), indirect tumor viruses modify the cellular context to facilitate changes in cell growth. For example, the virus can trigger immunodeficiency facilitating other carcinogenic events such as concurrent viral infection or chronic inflammation. For indirect oncogenic viruses, the disease association is determined by epidemiological data, experimental results explaining possible modes of virus-host interaction, and by clinical observations. The association between virus and cancer thus becomes more a question of plausibility than stringent experimental deduction.

Mechanisms of direct versus indirect causality

As mentioned above, human oncoviruses can cause tumors in two ways, direct or indirect. In the direct route, some viruses integrate their viral genome into that of the host cell. The integrated virus can activate nearby cellular oncogenes and/or inactivate tumor suppressor genes leading to cellular transformation with increased proliferative

fitness of the cell. Transformed cells have increased cell growth rates and loss of growth inhibition, a limitless replicative potential, and changes in cellular morphology and metabolism. However, the mechanisms used by different viruses to cause cancer are various and complex.

Persistent infection with directly transforming oncoviruses such as HPV 16 and 18 is accompanied by the integration of viral sequences into human chromosomes. This integration may disrupt the normal transcription of some genes such as the cellular oncogene *c-myc* [2] to cause cancer. EBV and HHV8 produce viral proteins with homology to known cellular proto-oncoproteins. These viral mimics of cellular proteins induce immune evasion, inhibit apoptosis, and change cell growth by affecting the expression of many host genes [11]. For HTLV-1, several studies have shown that the expression of viral Tax protein is necessary and sufficient to cause leukemia. Recent data suggest that *in vivo* carcinogenesis caused by Tax also correlates with its propensity to trigger tissue inflammation [12].

Indirect viral oncogenesis can also occur in various ways. Carcinogenesis can arise by immunosuppression and by chronic nonspecific inflammation occurring over decades. It is generally thought that HBV and HCV transform tissues indirectly through the induction of chronic inflammation in the affected liver perhaps *via* the production of reactive oxygen radicals. In a similar vein, HIV infection likely contributes indirectly to the development of KS cancers *via* immunosuppression [3].

Comorbidities and multistep progression in tumorigenesis

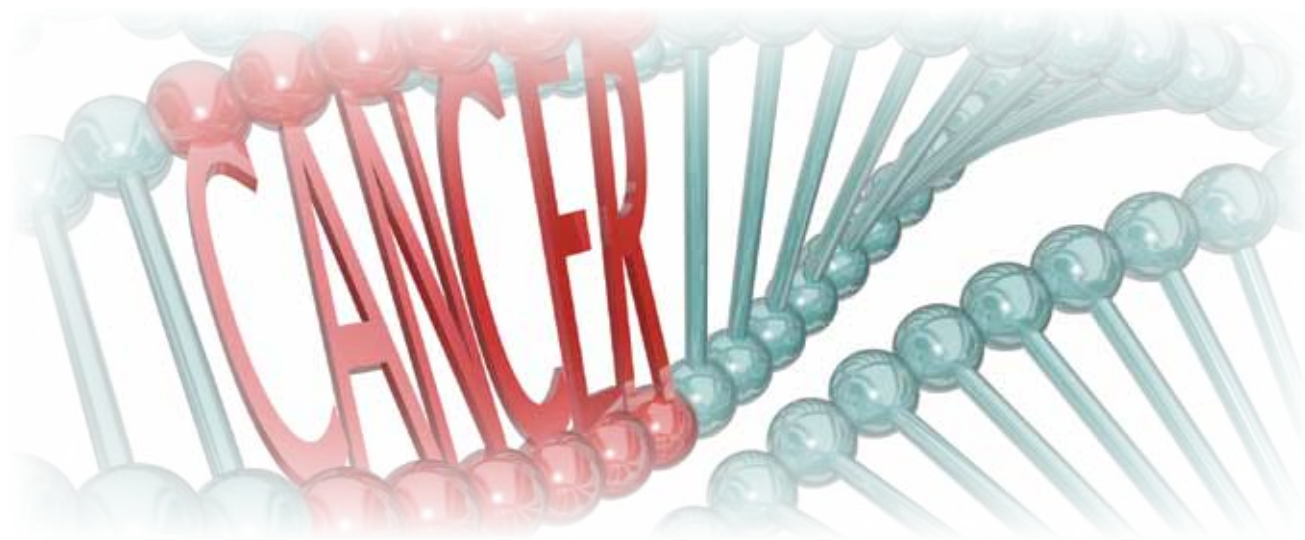
Oncoviral infection of cells are much more common than the cancers that arise from infected cells suggesting that infection *per se* is insufficient for tumor development and that tumorigenesis requires the contribution of several factors in a multistep process. Thus, the progression of HPV-associated squamous-cell epithelial lesions to cervical

cancer is enhanced by comorbid agents such as herpes simplex virus or Chlamydia or concurrent immunodeficiency. Other risk factors include smoking, high numbers of pregnancies, first pregnancy at young age, and use of oral contraceptive [3]. The immunosuppressive effects of malarial infection have been proposed to activate EBV-associated lymphoproliferation [6], and ambient exposure to potential carcinogens such as salted fish containing nitrosodimethylamines and perhaps inhaled herbal extracts have been implicated as possible cofactors in EBV-associated nasopharyngeal carcinoma. Similarly as noted above, HIV infection contributes to KS *via* immunosuppression. Accordingly, effective highly active antiretroviral therapy (HAART) of HIV has caused a decline in the incidence of KS in Western countries [5].

In a multistep process, only some infected cells will complete all the steps to achieve transformation. This notion fits with the observation that only a fraction of virus infected cells become cancerous. Indeed, a succession of changes which confer cell growth advantage is seen in the process of cellular transformation [13]. For example, some of these stepwise changes for leukemogenesis caused by HTLV-1 include damaged cellular chromosomal DNA and abnormal chromosome numbers (aneuploidy). Similar changes are also seen in HPV-transformed cells. However, a distinction exists amongst different oncogenic viruses; some act to simply initiate the transformation of cells while others are needed to initiate and maintain the transformed cells. Thus, sixty to seventy percent of late stage HTLV-1 induced ATLs appear to become virus independent leukemias that do not express viral proteins [12] while all late stage HPV cervical tumors still require the expression of two HPV oncoproteins, E6 and E7, for the maintenance of the cancer.

Unanswered questions and future challenges

Although HCC is the most common cancer associated with HCV infection, two other malignancies are also seen



with this virus. It has been suggested that HCV may also be a risk factor for the onset of cholangiocellular carcinoma. In HCV patients, the risk of cholangiocellular carcinoma is estimated to be increased by 2.6 times. Because cholangiocellular carcinoma and hepatocellular carcinoma may arise from the same progenitor cells, a common mechanism(s) may account for both types of malignant transformation [8]. The second HCV associated disease is cryoglobulinaemia (MC), a lymphoproliferative disease that can evolve into B-cell non-Hodgkin lymphoma (NHL). This pathology may be under-reported and possibly underdiagnosed in HCV-infected patients [8] because few studies have evaluated the association between HCV infection and NHL [3].

Several other associations between viral infections and human cancers remain to be considered. In primary central nervous

system (CNS) malignancies, polyomaviruses have been detected with varying frequencies in a number of pediatric and adult tumor subtypes. Three polyomaviruses that have been detected most frequently in both pediatric and adult primary CNS brain tumors are the JC virus (JCV), BK virus (BKV), and Simian virus 40 (SV40). However, actually establishing a link between chronic viral infection and primary CNS malignancy is an area of considerable controversy, due in part to variations in detection frequencies and methodologies used among researchers. Highlighting these difficulties are recent findings whereby a previously proposed link between SV40 and lung cancer now appears largely disproven [14, 15] and a reported association between XMRV and human prostate cancer appears also in doubt [16]. Both SV40 and XMRV are non-human animal viruses. While their roles in human cancers

are now mostly unsubstantiated, it remains possible that other animal viruses could in the future cross the species barrier to become new tumorigenic agents in humans.

Concluding remarks

Viral infections represent an area of cancer research which has made significant advances in the last 30 years. In 1981, only two viruses were thought to cause human cancers. Now, the oncogenic roles of eight viruses are well-established [17]. It is likely that many other viral infections that may be oncogenic in humans remain to be unveiled. Because oncogenic viral infection can be prevented with vaccines (safe and effective HBV and HPV vaccines have been developed), it is imperative that we redouble our efforts to identify and characterize viral etiologies of human neoplasias.

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