
Epidemiology of Virus Infection and Human Cancer

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Abstract

The International Agency for Research on Cancer (IARC) has comprehensively assessed the human carcinogenicity of biological agents. Seven viruses including Epstein–Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), Kaposi's sarcoma herpes virus (KSHV), human immunodeficiency virus, type-1 (HIV-1), human T cell lymphotropic virus, type-1 (HTLV-1), and human papillomavirus (HPV) have been classified as Group 1 human carcinogens by IARC. The conclusions are based on the findings of epidemiological and mechanistic studies. EBV, HPV, HTLV-1, and KSHV are direct carcinogens; HBV and HCV are indirect carcinogens through chronic inflammation; HIV-1 is an indirect carcinogen through immune suppression. Some viruses may cause more than one cancer, while some cancers may be caused by more than one virus. However, only a proportion of persons infected by these

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oncogenic viruses will develop specific cancers. A series of studies have been carried out to assess the viral, host, and environmental cofactors of EBV-associated nasopharyngeal carcinoma, HBV/HCV-associated hepatocellular carcinoma, and HPV-associated cervical carcinoma. Persistent infection and high viral load are important risk predictors of these virus-caused cancers. Risk calculators incorporating host and viral factors have also been developed for the prediction of long-term risk of hepatocellular carcinoma. These risk calculators are useful for the triage and clinical management of infected patients. Both clinical trials and national programs of immunization or antiviral therapy have demonstrated a significant reduction in the incidence of cancers caused by HBV, HCV, and HPV. Future researches on gene–gene and gene–environment interaction of oncogenic viruses and human host are in urgent need.

Keywords

Cancer • EBV • Epidemiology • HBV • HCV • HIV • HPV • HTLV-I • KSHV

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1 Introduction

The International Agency for Research on Cancer has comprehensively assessed the carcinogenicity of the biological agents to humans based on epidemiological and mechanistic evidence (IARC 2009). Seven viruses including Epstein–Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), Kaposi’s sarcoma herpes virus (KSHV), human immunodeficiency virus, type-1 (HIV-1), human T cell lymphotropic virus, type-1 (HTLV-1), and several types of human papillomavirus (HPV) have been classified as Group 1 human carcinogen as shown in the Table 1.

There is sufficient evidence to conclude that EBV causes nasopharyngeal carcinoma, Burkitt’s lymphoma, immune suppression-related non-Hodgkin lymphoma, extranodal NK/T cell lymphoma (nasal type), and Hodgkin’s lymphoma in humans. The evidence for EBV-caused gastric carcinoma and lympho-epithelioma-like carcinoma is limited. HBV and HCV cause hepatocellular carcinoma

Table 1 Cancers caused by Group 1 oncogenic viruses with sufficient and limited evidence according to the IARC criteria

Virus	Cancer sites with sufficient evidence	Cancer sites with limited evidence
Epstein–Barr virus (EBV)	Nasopharyngeal carcinoma, Burkitt's lymphoma, immune suppression-related non-Hodgkin lymphoma, extranodal NK/T cell lymphoma (nasal type), Hodgkin's lymphoma	Gastric carcinoma, lympho-epithelioma-like carcinoma
Hepatitis B virus (HBV)	Hepatocellular carcinoma	Cholangiocarcinoma, non-Hodgkin lymphoma
Hepatitis C virus (HCV)	Hepatocellular carcinoma, non-Hodgkin lymphoma	Cholangiocarcinoma
Human immunodeficiency virus, type 1 (HIV-1)	Kaposi's sarcoma, non-Hodgkin lymphoma, Hodgkin's lymphoma, cancers of the cervix, anus, and conjunctiva	Cancers of the vulva, vagina and penis, non-melanoma skin cancer, hepatocellular carcinoma
Human papillomavirus type 16 (HPV-16)	Cancers of the cervix, vulva, vagina, penis, anus, oral cavity, oropharynx, and tonsil	Cancer of the larynx
Human papillomavirus type 18, 31, 33,35, 39, 45, 51, 52, 56, 58, 59 (HPV-18, 31, 33,35, 39, 45, 51, 52, 56, 58, and 59)	Cancer of the cervix	
Human papillomavirus type 26, 30, 34, 53, 66, 67, 68, 69, 70, 73, 82, 85, 97 (HPV- 26, 30, 34, 53, 66, 67, 68, 69, 70, 73, 82, 85, and 97)		Cancer of the cervix
Human T cell lymphotropic virus, type-1 (HTLV-1)	Adult T cell leukemia and lymphoma	
Kaposi's sarcoma herpes virus (KSHV)	Kaposi's sarcoma, primary effusion lymphoma	Multicentric Castleman's disease

with sufficient evidence. The evidence for HCV-caused non-Hodgkin lymphoma, especially B-cell lymphoma, is sufficient, while the evidence for HBV-caused non-Hodgkin lymphoma is limited. There is also limited evidence to conclude that HBV and HCV cause cholangiocarcinoma. The evidence to conclude that HIV-1 causes Kaposi's sarcoma, non-Hodgkin lymphoma, Hodgkin's lymphoma, and cancers of the cervix, anus, and conjunctiva is sufficient. But the evidence for HIV-1 to cause cancers of the vulva, vagina, penis, non-melanoma skin cancer, and hepatocellular carcinoma is limited.

There is sufficient evidence to conclude that HPV-16 causes cancers of the cervix, vulva, vagina, penis, anus, oral cavity, oropharynx, and tonsil; but the evidence for HPV-16 to cause cancer of the larynx is limited. Cervical cancer is caused by several types of HPV including HPV-18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. The evidence for HPV-26, 30, 34, 53, 66, 67, 68, 69, 70, 73, 82, 85, and 97 to cause cervical cancer is limited. HTLV-1 causes adult T cell leukemia and lymphoma with sufficient evidence. There is sufficient evidence to conclude KSHV causes Kaposi's sarcoma and primary effusion lymphoma, but the evidence for KSHV to cause multicentric Castleman's disease is limited.

The proportion of cancers caused by infectious agents was recently estimated to be more than 20 % (IARC 2009). The identification of new cancer sites attributed to these agents means that more cancers are potentially preventable. This chapter will review mainly the epidemiology of oncogenic viruses and their associated cancers.

2 Prevalence of Oncogenic Virus Infection in the World

EBV is highly prevalent throughout the world with more than 90 % adults infected with EBV even in the remote populations (IARC 2009). The estimated number of persons infected with EBV is more than 5.5 billion. The age at primary infection of EBV varies significantly in the world. People live in overcrowded conditions with poor sanitation have a younger age at primary infection than those live in better environments. Two major types of EBV have been identified and differ in geographical distribution with EBV-2 more common in Africa and homosexual men. The role of specific EBV types in the development of difference cancers remains to be elucidated. As EBV infection is ubiquitous, the specific geographical distribution of EBV-related malignancies including endemic Burkitt lymphoma and nasopharyngeal carcinoma is more likely attributable to the variation in the distributions of other cofactors which may activate EBV replication.

Figure 1 shows the geographical variation in the prevalence of oncogenic viruses in the world. HBV infects more than 2.0 billion people in the world and more than 300 million of them are chronic HBV carriers (IARC 2009). There is a wide variation of chronic HBV infection in the world¹ as shown in Fig. 1a. Approximately 45 %, 43 %, and 12 % of the world population live in areas where the endemicity of chronic HBV infection is high (seroprevalence of hepatitis B surface antigen >8 %), medium (2–7 %), and low (<2 %). The prevalence is highest in sub-Saharan Africa, the Amazon Basin, China, Korea, Taiwan, and several countries in Southeast Asia. In areas of high endemicity, the lifetime risk of HBV infection is more than 60 % with most infections acquired from perinatal and child-to-child transmission, when the risk of becoming chronic infection is greatest. Perinatal (vertical) transmission is predominant in China, Korea, and

¹ CDC <http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/hepatitis-b.htm>

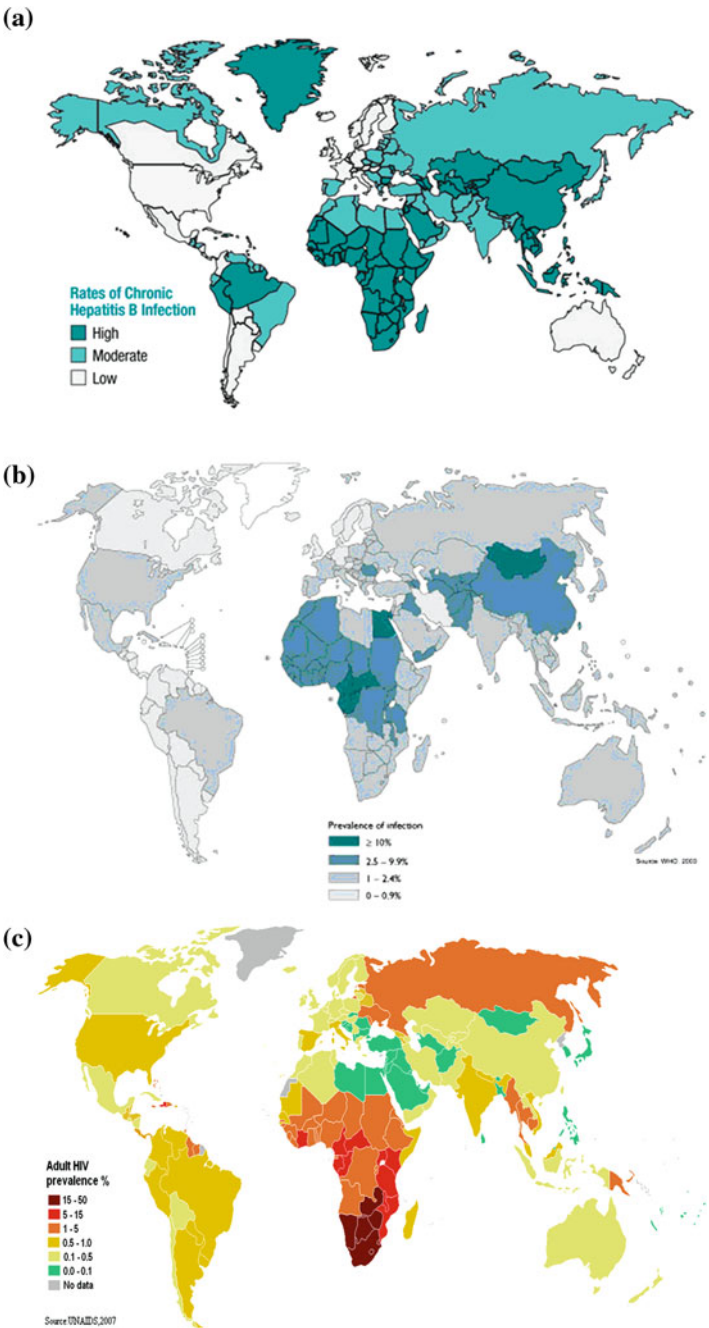


Fig. 1 Estimated prevalence (per 100) of Group 1 oncogenic viruses in the world. **a** HBV, **b** HCV, **c** HIV-1, **d** HPV, **e** HTLV-1, and **f** KSHV

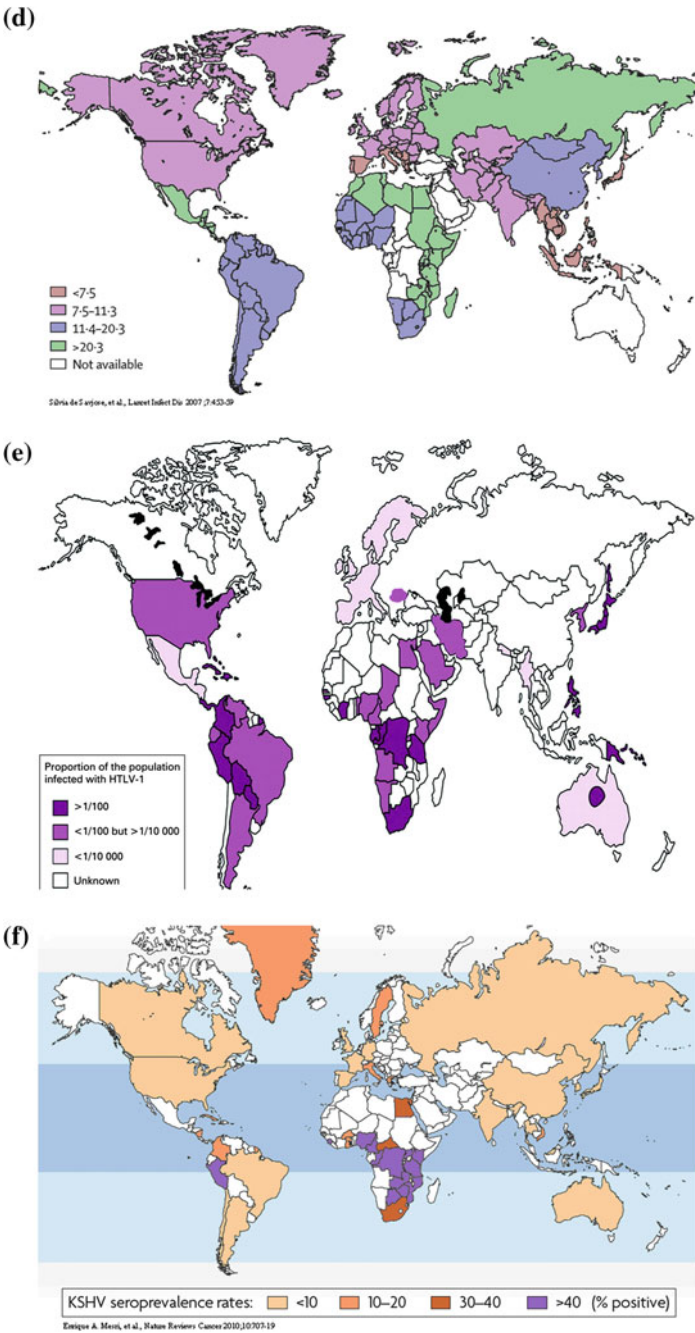


Fig. 1 (continued)

Taiwan where the seroprevalence of HBeAg in pregnant women is high, while child-to-child (horizontal) transmission is common in sub-Saharan Africa where HBeAg seroprevalence is low in mothers. In areas of medium endemicity, mixed HBV transmission patterns occur in infancy, early childhood, adolescence, and adulthood. In the low endemicity areas, most HBV infections occur in adolescents and young adults through injection drug use, male homosexuality, health care practice, and regular transfusion or hemodialysis.

In addition to the striking geographical variation in seroprevalence of HBsAg in the world, the distribution of eight genotypes of HBV varies significantly in different countries (IARC 2009). Genotype A is prevalent in Europe, Africa, and North America; genotypes B and C are prevalent in East and Southeast Asia; Genotype D is predominant in South Asia, Middle East, and Mediterranean areas; genotype E is limited to West Africa; genotypes F and G are found in Central and South America; and genotype H is observed in Central America.

HCV infects around 150 million people in the world showing an estimated prevalence of 2.2 % (IARC 2009) with a wide variation in different regions as shown in Fig. 1b. The estimates of HCV infection (seroprevalence of antibodies against HCV) range from <0.1 % in the United Kingdom and Scandinavia to 15–20 % in Egypt (Alter 2007). The high prevalence of HCV infection was observed in Mongolia, northern Africa, Pakistan, China, southern Italy, and some areas in Japan. There are at least six major genotypes of HCV have been identified. There is a wide variation in geographical distribution of HCV genotype in the world. The response to antiviral therapy also varies by HCV genotype. It is better in patients infected with genotype 2 or 3 than those with genotype 1 or 4.

HCV have two major transmission routes including injection drug use and iatrogenic exposures through transfusion, transplantation, and unsafe therapeutic injection. While iatrogenic transmission of HCV has been reduced after 1990 in developed countries such as Japan and Italy, it remains frequent in low-resource countries where disposable needles tend to be reused. Injection drug use is the most important transmission route for newly acquired HCV infection in developed countries. Transmission of HCV through perinatal, sexual, and accidental needle-stick exposures is less efficiently than iatrogenic exposure and injection drug use.

HIV infects estimated 34 million people in the world at the end of 2010 (IARC 2009).² An estimated 0.8 % of adults aged 15–49 years worldwide are living with HIV, and the burden varies considerably between countries and regions as shown in Fig. 1c. Sub-Saharan Africa remains most severely affected with a prevalence of 4.9 %. Although the prevalence of HIV infection is nearly 25 times higher in sub-Saharan Africa than in Asia, almost 5 million people are living with HIV in South, Southeast, and East Asia combined. After sub-Saharan Africa, regions most heavily affected are the Caribbean and Eastern Europe and Central Asia, where 1.0 % of adults were living with HIV in 2011. There were 2.5 million people including 0.39 million children were newly infected with HIV in 2011. Since

² UNAIDS http://data.unaids.org/pub/epislides/2012/2012_epiupdate_en.pdf

2001, annual HIV incidence has fallen in 33 countries, 22 of them in sub-Saharan Africa. However, incidence is accelerating again in Eastern Europe and Central Asia after having slowed in the early 2000s, and new infections are on the rise in the Middle East and North Africa.

HIV-1 infection is transmitted through three major routes: sexual intercourse, blood contact, and mother-to-child transmission. The HIV-1 infectivity is determined by the interaction of three factors of agent, host, and environments. The probability of HIV-1 transmission is highest for blood transfusion, followed by mother-to-child transmission, needle sharing, man-to-man sexual transmission, and lowest for woman-to-man sexual transmission.

HPV infection is very prevalent in most sexually active individuals will acquire at least one genotype of anogenital HPV infection during their lifetime (IARC 2009). The estimated oncogenic HPV DNA point prevalence has been reported as high as 10 % in a meta-analysis of 157,879 women with normal cytology, giving an estimate of 600 million people being infected (de Sanjose et al. 2007). The point prevalence was highest (20–30 %) in Africa, East Europe, and Latin America; and lowest (6–7 %) in southern and western Europe and Southeast Asia demonstrating a striking geographical variation as shown in Fig. 1d. The estimated point prevalence is highly dynamic because both incidence and clearance rates are high.

Among 13 oncogenic HPV types, the most prevalent types include 16, 18, 31, 33, 35, 45, 52, and 58. HPV 16 is the most common type in all regions with prevalence ranging 2.3–3.5 %. HPV infections are transmitted through direct skin-to-skin or skin-to-mucosa contact. Anogenital HPV types spread mainly through sexual transmission in teenagers and young adults. Non-sexual routes including perinatal and iatrogenic transmissions account for a minority of HPV infections.

HTLV-1 infects estimated 15–20 million people in the world (IARC 2009). HTLV-1 infection is characterized by the micro-epidemic hotspots surrounded by low prevalence areas as shown Fig. 1e (Proietti et al. 2005). The HTLV-1 infection prevalence ranges from <0.1 % in China, Korea, and Taiwan to 20 % in Kyushu and Okinawa of Japan. The regions of high endemicity include south-western Japan, parts of sub-Saharan Africa, the Caribbean Islands, and South Africa. HTLV-1 has three major transmission routes: vertical transmission, sexual transmission, and parenteral transmission. Vertical transmission through breast-feeding has a high efficiency to result in mother-to-child infection. However, in utero infectivity is low due to limited trafficking of HTLV-1-infected lymphocytes across placenta. The efficiency of sexual transmission of HTLV-1 depends on the proviral load and use of condom. Parenteral transmission through transfusion is significantly reducing due to the sensitive serological examination of blood products. Needle sharing associated with injection drug use is another parenteral route for HTLV-1 transmission.

Infection prevalence of KSHV determined by serological tests varies significantly in the world (Dukers and Rezza 2003) as shown in Fig. 1f. It ranges from 2–3 % in northern Europe to 82 % in Congo (IARC 2009). The prevalence is generally low (<10 %) in northern Europe, the USA, and Asia, elevated in

Mediterranean region (10–30 %) and high in sub-Saharan Africa (>50 %). The KSHV is primarily transmitted via saliva. In the countries where KSHV prevalence is high, the infection occurs during childhood and increases with age. The transmission of KSHV among homosexual men is also via saliva. KSHV may also be transmitted with a low efficiency through prolonged injection drug use, blood transfusion, and organ transplantation.

3 Incidence of Some Virus-caused Cancers in the World

The world maps of age-adjusted incidence rates of some oncogenic virus-related cancers are shown in Fig. 2. The age-adjusted incidence rates of nasopharyngeal cancer range from <0.1 to 8.05 per 100,000 as shown in Fig. 2a. The highest incidence was observed in southern China, Southeast Asia, and sub-Saharan Africa, and the lowest incidence in Europe, western Africa, and Central America. Chinese ethnicity in different cancer registries has the highest incidence of nasopharyngeal cancer. As EBV infection is ubiquitous in humans, the uniquely high incidence of nasopharyngeal carcinoma suggesting Chinese lifestyles or genetic susceptibility may play an important role in the development of nasopharyngeal cancer.

The age-adjusted incidence rates of Burkitt lymphoma are shown in Fig. 2b. Central Africa, equatorial South America, Papua New Guinea, and Caribbean countries are endemic for Burkitt lymphoma, but the incidence rate of Burkitt Lymphoma is relatively low in other countries. As EBV infection is ubiquitous in humans, the extraordinarily high endemicity of Burkitt lymphoma in Africa suggesting local environments or genetic susceptibility may play an important role in the development of endemic Burkitt lymphoma.

The age-adjusted incidence rates of liver cancer range from 0.70 to 94.4 per 100,000 as shown in Fig. 2c. The highest incidence was observed in East Asia, Southeast Asia, Egypt, and sub-Saharan Africa, and the lowest incidence in Europe, Middle East, Australia, New Zealand, and Canada. The geographical variation in liver cancer incidence is consistent with that of seroprevalence of HBV and HCV.

The age-adjusted incidence rates of cervical cancer range from 2.14 to 56.29 per 100,000 as shown in Fig. 2d. The highest incidence was observed in Latin America, South Asia, and sub-Saharan Africa, and the lowest incidence in Europe, North America, Australia, New Zealand, and Middle East. The geographical variation in cervical cancer incidence is consistent with that of seroprevalence of oncogenic HPV.

The age-adjusted incidence rates of Kaposi's sarcoma range from <1.0 to 30 per 100,000 as shown in Fig. 2e. The highest incidence was observed in sub-Saharan Africa and the lowest incidence in Europe, Australia, North America, and East Asia. The geographical variation in Kaposi's sarcoma incidence is consistent with that of seroprevalence of KSHV.

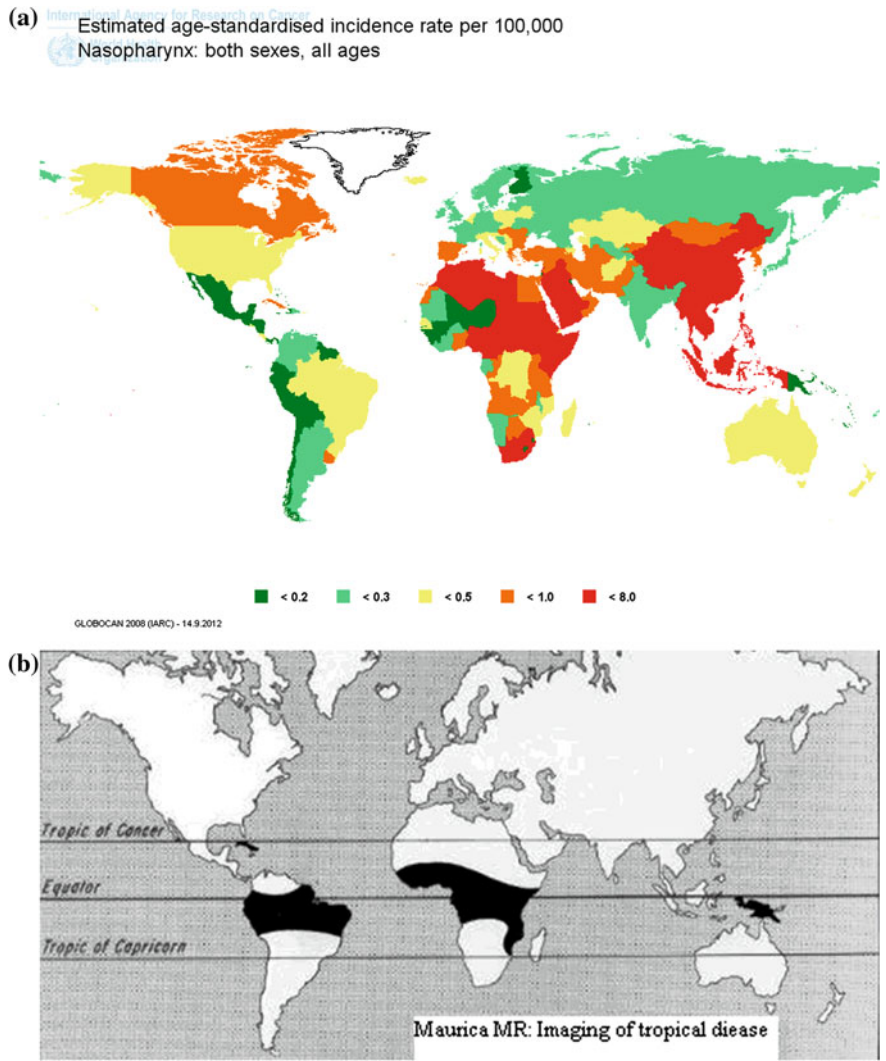


Fig. 2 Age-standardized incidence rate (per 100,000) of virus-caused cancers in the world. **a** Nasopharynx, **b** Burkitt lymphoma **c** Liver, **d** Cervix uteri, and **e** Kaposi’s sarcoma

4 Carcinogenic Mechanisms of Oncogenic Viruses

There are three major mechanisms of carcinogenesis for seven Group 1 oncogenic viruses as shown in Table 2. They are defined as direct, indirect through chronic inflammation, and indirect through immune suppression (IARC 2009). The direct carcinogens include EBV, HPV, HTLV-1 and KSHV; the indirect carcinogens

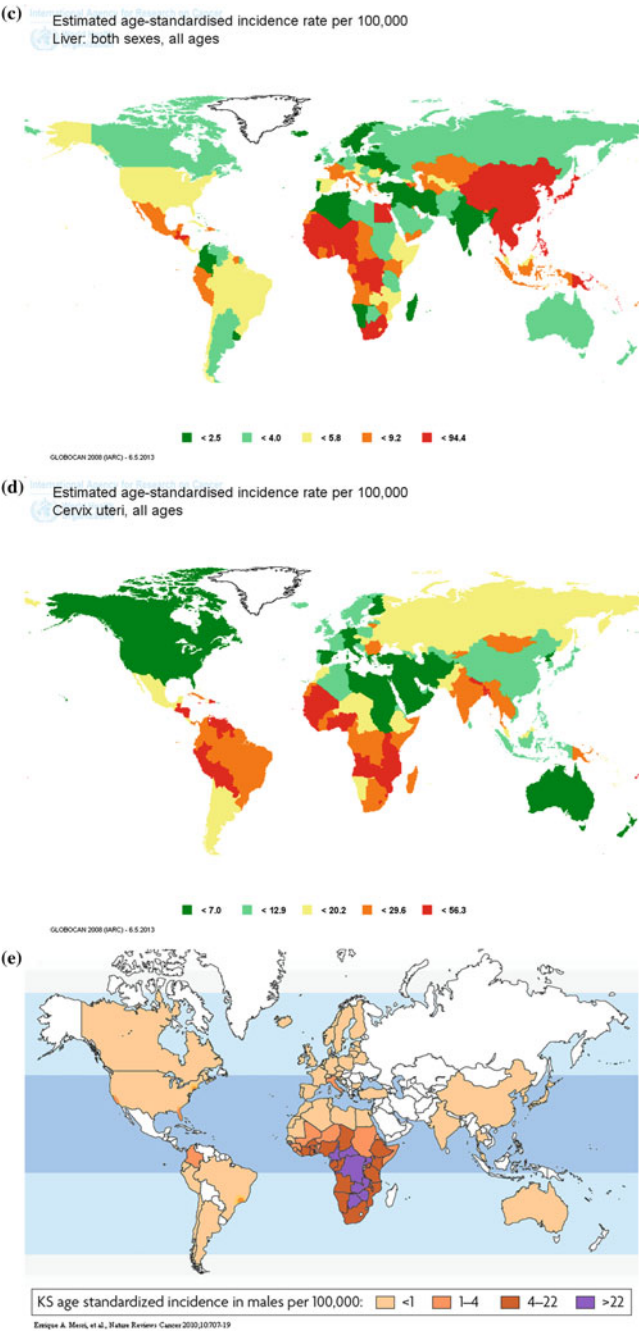


Fig. 2 (continued)

Table 2 Established carcinogenic mechanisms of oncogenic viruses

Mechanism	Group 1 virus (carcinogenic properties)
Direct	EBV (cell proliferation, inhibition of apoptosis, genomic instability, cell migration)
	HPV (immortalization, genomic instability, inhibition of DNA damage response, anti-apoptotic activity)
	HTLV-1 (immortalization and transformation of T cells)
	KSHV (cell proliferation, inhibition of apoptosis, genomic instability, cell migration)
Indirect through chronic inflammation	HBV (inflammation, liver cirrhosis, chronic hepatitis)
	HCV (inflammation, liver cirrhosis, liver fibrosis)
Indirect through immune suppression	HIV-1 (immunosuppression)

through chronic inflammation include HBV and HCV; and the indirect carcinogen through immune suppression is HIV-1.

Direct oncogenic viruses have following characteristics: (1) The entire or partial viral genome can usually be detected in each cancer cell. (2) The virus can immortalize after the growth of target cells in vitro. (3) The virus expresses several oncogenes that interact with cellular proteins to disrupt cell-cycle checkpoints, inhibit apoptosis, and DNA damage response, cause genomic instability, and induce cell immortalization, transformation, and migration.

Both HBV and HCV cause hepatocellular carcinoma through chronic inflammation, which leads to the production of chemokines, cytokines, and prostaglandins secreted by infected cells and/or inflammatory cells. The chronic inflammation also leads to the production of reactive oxidative species with direct mutagenic effects to deregulate the immune system and promote angiogenesis, which is essential for the neovascularization and survival of tumors.

Individuals infected with HIV-1 have a high risk of cancers caused by another infectious agent. HIV-1 infection, mainly through immunosuppression, leads to increased replication of oncogenic viruses such as EBV and KSHV. Although antiretroviral therapy lowers the risk of many cancers associated with HIV-1, risks remain high worldwide.

5 Lifetime Cumulative Incidence of Some Virus-caused Cancers

Some viruses may cause more than one cancer, while some cancers may be caused by more than one virus. However, only a proportion of persons infected by these oncogenic viruses will develop specific cancers. Table 3 shows the lifetime cumulative incidence of some virus-caused cancers. The cumulative lifetime

Table 3 Lifetime cumulative incidence and risk cofactors of virus-caused cancers

Virus (cancer)	Lifetime incidence	Viral factors	Host factors	Environmental factor
EBV (nasopharyngeal carcinoma)	Men, 2.0 %.	Elevated serotiter of antibodies against EBV, EBV viral load	Male gender, family history, genetic polymorphisms (xenobiotic metabolism, DNA repair, human leukocyte antigen)	Cantonese salted fish, Dietary nitrosamine, wood dust, formaldehyde, tobacco
HBV (hepatocellular carcinoma)	Men, 27.4 %; women, 8.0 %.	Persistent infection, viral load, genotype, mutant, serum HBsAg level	Elder age, male gender, obesity, diabetes, serum androgen and ALT level, family history, genetic polymorphisms (DNA repair, human leukocyte antigen, androgen, and xenobiotic metabolism)	Aflatoxins, alcohol, tobacco, carotenoids, selenium, HCV infection
HCV (hepatocellular carcinoma)	Men, 23.7 %; women, 16.7 %	Persistent infection, viral load, genotype, mutant	Elder age, male gender, obesity, diabetes, serum ALT level, family history, genetic polymorphisms	Alcohol, tobacco, betel, HBV or HTLV-1 infection, radiation
HPV (cervical carcinoma)	HPV-16, 34.3 %; HPV-52, 23.3 %; HPV-58, 33.4 %; Any oncogenic HPV, 20.3 %.	Persistent infection, viral load, genotype	Elder age, number of pregnancies, family history, serum estrogen level, genetic polymorphisms (DNA repair, human leukocyte antigen)	Tobacco, immunosuppression, HIV-1 infection, contraceptives, nutrients

(30–75 years old) risk of developing nasopharyngeal carcinoma was 2.2 % for men seropositive for IgA antibodies against EBV VCA or antibodies against EBV DNase and 0.48 % for those seronegative for both antibodies.

Only around one-quarter of patients with patients chronically infected with HBV will develop hepatocellular carcinoma showing a striking gender difference of 27.4 % for men and 8.0 % for women (Huang et al. 2011). The development of hepatocellular carcinoma caused by HBV has been considered as a multistage hepatocarcinogenesis with multifactorial etiology, which involved the interaction

of HBV, chemical carcinogens, host characteristics, and genetic susceptibility (Chen et al. 1997; Chen and Chen 2002; Chen and Yang 2011; IARC 2009).

Around one-fifth of patients seropositive for antibodies against HCV (anti-HCV) will develop hepatocellular carcinoma showing a less significant gender difference of 23.7 % for men and 16.7 % for women (Huang et al. 2011). The lifetime cumulative risk of HCC for anti-HCV seropositives with and without detectable serum HCV RNA level was 3.53 % and 24.2 %, respectively. Many cofactors have been involved in the development of hepatocellular carcinoma in anti-HCV seropositives (Lee et al. 2010; IARC 2009).

The cumulative lifetime (30–75 years old) risk of cervical cancer for women who were infected by HPV16, HPV 52, HPV 58, and any Group 1 oncogenic HPV was 34.3 %, 23.3 %, 33.4 %, and 20.3 %, respectively. Women with persistent oncogenic HPV infection have a much higher cumulative risk of cervical cancer than those with the transient infection (Chen et al. 2011b).

6 Cofactors of Some Virus-caused Cancers

Only a proportion of persons infected by oncogenic viruses will develop specific cancers. The fact strongly suggests the involvement of cofactors in the oncogenic process. Carcinogenesis would result from the interaction of multiple risk factors including viral factors, host factors, and environmental factors as shown in Table 3. The viral factors include various infection markers such as viral load, genotypes, variants, mutants, and serotiter of antibodies. The host factors include age, gender, race, anthropometric characteristics, immune status, hormonal level, personal disease history, and family cancer history. The environmental factors include chemical carcinogens, nutrients, ionizing radiation, immunosuppressive drugs, and coinfections of other infectious agents. The contribution of several additional factors to the development of virus-associated cancers seems to be substantial, but has not yet been elucidated in detail.

Several cofactors for nasopharyngeal carcinoma have been reviewed previously (Chien and Chen 2003). The viral factors associated with EBV-caused nasopharyngeal carcinoma include the elevated serotiter of antibodies against EBV including anti-EBV VCA IgA, anti-EBV DNase, anti-EBNA1 (Chien et al. 2001; Hsu et al. 2009), and the elevated serum EBV DNA level (viral load). Host factors include male gender, family history of nasopharyngeal carcinoma (Hsu et al. 2011), and genetic polymorphisms of xenobiotic metabolism enzymes (Hildesheim et al. 1997), DNA repair enzymes (Cho et al. 2003), and human leukocyte antigen (Hildesheim et al. 2002; Hsu et al. 2012b). Environmental factors include consumption of Cantonese salted fish, high dietary intake of nitrite and nitrosamine (Ward et al. 2000), occupational exposure to wood dust and formaldehyde (Hildesheim et al. 2001), long-term tobacco smoking (Hsu et al. 2009), and low intake of plant vitamin, fresh fish, green tea, and coffee (Hsu et al. 2012a).

The viral factors associated with HBV-caused hepatocellular carcinoma include the elevated serum level HBeAg serostatus (Yang et al. 2002), serum HBV DNA level (Yang et al. 2002; Chen et al. 2006; Chen et al. 2009), HBV genotype and mutant types (Yang et al. 2008), and elevated serum HBsAg level (Lee et al. 2013). Host factors include elder age, male gender, elevated serum alanine aminotransferase (ALT) level, family history of hepatocellular carcinoma (Chen et al. 1991; Yu et al. 2000a; Yang et al. 2010), disease status of obesity and diabetes (Chen et al. 2008), elevated serum level of androgen and androgen-related genetic polymorphisms (Yu and Chen 1993; Yu et al. 2000b), and genetic polymorphisms of xenobiotic metabolism enzymes and DNA repair enzyme (Chen et al. 1996a; Yu et al. 1995a, 1999a, 2003). Environmental factors include aflatoxin exposure (Chen et al. 1996b; Wang et al. 1996), habits of alcohol consumption and tobacco smoking (Chen et al. 1991; Wang et al. 2003), inadequate intake of carotenoids and selenium (Yu et al. 1995b, 1999a, b), and coinfection with HCV (Huang et al. 2011).

The viral factors associated with HCV-caused hepatocellular carcinoma include the elevated serum level of HCV RNA and HCV genotype 1 (Lee et al. 2010; Huang et al. 2011). Host factors include elder age, male gender, obesity, diabetes, elevated serum ALT level, family history of hepatocellular carcinoma, and genetic polymorphisms (Sun et al. 2003; Chen et al. 2008; Lee et al. 2010; IARC 2009). Environmental factors include alcohol consumption, tobacco smoking, betel hewing, radiation exposure, and coinfection with HBV or HTLV-1 (Sun et al. 2003; Huang et al. 2011; IARC 2009).

The viral factors associated with oncogenic HPV-caused cervical cancer include the persistent infection, elevated viral load, HPV genotypes, and variants (Chen et al. 2011a, b; Chang et al. 2011; IARC 2009). Host factors include elder age, number of pregnancies, family history of cervical cancer, serum estrogen level, genetic polymorphisms of DNA repair enzymes, and human leukocyte antigen (Chen et al. 2011a; Chuang et al. 2012; IARC 2009). Environmental factors include tobacco smoking, immunosuppression, HIV-1 coinfection, use of oral contraceptives, and inadequate intake of micronutrients (IARC 2009).

7 Risk Calculators of HBV-caused Hepatocellular Carcinoma

As there are many risk predictors for each virus-caused cancer, it is useful to incorporate all these factors to develop a risk model or risk calculator for the prediction of cumulative cancer incidence. Such risk calculators may provide clinicians important information for the triage of patients who need intensive treatment from those who need only routine follow-up. Several risk models/calculators have been developed to predict the incidence of hepatocellular carcinoma of chronic hepatitis B patients (Yang et al. 2010), and only REACH-B score was externally validated (Yang et al. 2011). The REACH-B score has recently been used to examine the efficacy of antiviral therapy to reduce liver cancer risk of chronic hepatitis B patients.

Table 4 Scores assigned to risk predictors of HBV-caused hepatocellular carcinoma

Risk predictor	Risk score
Age	
30–34	0
35–39	1
40–44	2
45–49	3
50–54	4
55–59	5
60–64	6
Sex	
Female	0
Male	2
Family history of hepatocellular carcinoma	
No	0
Yes	2
Serum ALT levels (IU/L)	
<15	0
15–44	1
≥45	2
HBeAg/HBV DNA (copies/mL)/HBsAg (IU/mL)/Genotype	
Negative/<10 ⁴ / <lt;100 any="" td="" type<=""><td>0</td></lt;100>	0
Negative/<10 ⁴ /100–999/any type	2
Negative/<10 ⁴ /≥1000/any type	2
Negative/10 ⁴ –10 ⁶ / <lt;100 any="" td="" type<=""><td>3</td></lt;100>	3
Negative/10 ⁴ –10 ⁶ /100–999/any type	3
Negative/10 ⁴ –10 ⁶ /≥1000/any type	4
Negative/≥10 ⁶ /any level/B or B + C	5
Negative/≥10 ⁶ /any level/C	7
Positive/any level/any level/B or B+C	6
Positive/any level/any level/C	7

Table 4 shows a most recent HCC risk calculator for chronic hepatitis B patients (Lee et al. 2013). Predictors included in the risk calculator are age, gender, family history of hepatocellular carcinoma, serum ALT level, HBeAg serostatus, serum levels of HBV DNA and HBsAg, and HBV genotype. Risk scores are

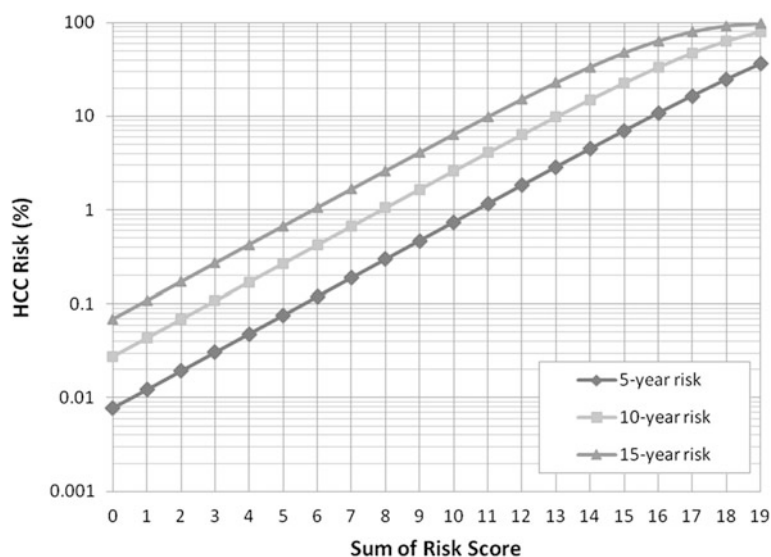


Fig. 3 Nomogram for predicted 5-, 10-, and 15-year risk of hepatocellular carcinoma by sum of risk score

assigned for various categories of risk predictors. For example, a 60-year-old (risk score = 6) male (risk score = 2) chronic hepatitis B patient who had a family history of hepatocellular carcinoma (risk score = 2), a serum ALT level of 90 IU/L (risk score = 2), a HBeAg-seropositive serostatus, a serum HBV DNA level of 10^7 copies/mL, a serum HBsAg level of 104 IU/mL, and a HBV genotype C infection (risk score = 7) has a sum of risk score of 19. The 5-, 10-, and 15-year cumulative risks of hepatocellular carcinoma by the sum of risk score are shown in the nomogram of Fig. 3. For the patient with a sum of risk score as high as 19, his 5- and 10- and 15-year risk of hepatocellular carcinoma will be 35 %, 80 %, and 90 %. In contrast, a 34-year-old women with no family history of hepatocellular carcinoma, a serum ALT level of 10 IU/L, a HBeAg-negative serostatus, a serum HBV DNA level of 10^3 copies/mL, and a serum HBsAg level of 50 IU/mL (sum of risk score = 0) has 5-, 10-, and 15-year risk of hepatocellular carcinoma of 0.0075 %, 0.025 %, and 0.065 %.

The risk calculators for other virus-caused cancers such as nasopharyngeal carcinoma and cervical cancer may also be helpful to improve the triage and clinical management of patients infected with other oncogenic viruses. The development of the risk calculators needs large-scale prospective cohorts, which have been followed for a long period of time with accurate measurements of risk predictors. Demographical characteristics, viral infection biomarkers, family history, and polymorphisms of genetic susceptibility may be incorporated to develop valid and useful cancer risk calculators.

Table 5 Evidence showing the reduction of incidence of virus-caused cancers through the preventive strategy of vaccination and antiviral therapy

Virus	Cancer	Preventive strategy
HBV	Hepatocellular carcinoma	Vaccination and antiviral therapy
HCV	Hepatocellular carcinoma	Antiviral therapy
HIV-1	Kaposi's sarcoma	Antiviral therapy
HPV	Cervical cancer	Vaccination

8 Cancer Incidence Reduction through Vaccination and Antiviral Therapy

The most effective strategy to prevent virus-caused cancers is through the vaccination to prevent viral infection or the antiviral therapy to eliminate oncogenic viruses in human host. Table 5 shows currently available vaccines or antivirals to prevent or treat patients with oncogenic viral infection. Vaccines are available for the prevention of HBV-caused hepatocellular carcinoma and HPV-caused cervical cancer, while antiviral therapies are available for the treatment of chronic infection of HBV, HCV, and HIV.

Many clinical trials have demonstrated the efficacy of the HPV vaccination to prevent cervical neoplasia, the precursor lesions of cervical cancer, and the efficacy of antiviral therapy to prevent hepatocellular carcinoma in cirrhotic patients (Liaw et al. 2004). The national HBV immunization program in Taiwan implemented in 1984 has successfully reduced the incidence of hepatocellular carcinoma at ages 6–19 years in vaccinated birth cohorts (Chang et al. 1997, 2009; Chien et al. 2006). The HPV immunization program in Australia has effectively lowered the incidence of cervical neoplasia in vaccinated adolescent cohorts. A national antiviral therapy program was implemented in 2003 to control chronic hepatitis B or C in Taiwan. It is expected to reduce the incidence and mortality of hepatocellular carcinoma in treated adult patients. However, its efficacy to prevent hepatocellular carcinoma remains to be assessed.

9 Future Perspectives

Along with the advancement in proteomic and genomic medicine, more and more biomarkers associated with the development of virus-caused cancers have been identified. They may be applied for the risk prediction or early detection of the cancers. For example, multiple micro RNAs have been combined for the diagnosis of hepatocellular carcinoma. However, its efficacy and cost-effectiveness for early diagnosis of HCC should be further assessed and compared with those of other methods including abdominal ultrasonography (Chen and Lee 2011). More

importantly, repeated measurements of biomarkers may further improve the risk prediction or early detection of virus-caused cancers (Chen 2005). For example, the trajectory of serum HBV DNA levels has been found to predict long-term risk of hepatocellular carcinoma effectively (Chen et al. 2011c). More longitudinal studies with regular follow-up examinations of various biomarkers are in urgent need to identify good molecular targets for the development of preventives, diagnostics, or therapeutics of various virus-caused cancers. The health economic assessment of these biopharmaceuticals may help the clinical application of them.

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