STATE-OF-THE-ART REVIEW

Infection and Cancer: Global Distribution and Burden of Diseases

Jin-Kyoung Oh, PhD, MPH, and Elisabete Weiderpass, PhD, MD

ABSTRACT

Background: Infection is one of the main risk factors for cancer.

Objectives: Epidemiology, pathogenesis, and disease burden of infection-related cancers were reviewed by infectious agents.

Findings: Chronic infection with Epstein-Barr virus, hepatitis B and C viruses, Kaposi sarcoma herpes virus, human immunodeficiency virus (HIV) type 1, human papillomavirus (HPV), human T-cell lymphotropic virus type 1, *Helicobacter pylori*, *Clonorchis sinensis*, *Opisthorchis viverrini*, and *Schistosoma haematobium* are associated with nasopharyngeal carcinoma; lymphoma and leukemia, including non-Hodgkin lymphoma, Hodgkin lymphoma, and Burkitt lymphoma; hepatocellular carcinoma; Kaposi sarcoma; oropharyngeal carcinoma; cervical carcinoma and carcinoma of other anogential sites; adult T-cell leukemia/lymphoma; gastric carcinoma; cholangiocarcinoma; and urinary bladder cancer. In 2008, approximately 2 million new cancer cases (16%) worldwide were attributable to infection. If these infections could be prevented and/or treated, it is estimated that there would be about 23% fewer cancers in less developed regions of the world, and about 7% fewer cancers in more developed regions.

Conclusion: Widespread application of existing public health methods for the prevention of infection, such as vaccination, safer injection practices, quality-assured screening of all donated blood and blood components, antimicrobial treatments, and safer sex practices, including minimizing one's lifetime number of sexual partners and condom use, could have a substantial effect on the future burden of cancer worldwide.

Key Words: burden, cancer, infection, vaccination

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INTRODUCTION

Infection is one of the main contributors to cancer development. Eleven biological agents have been identified as group 1 carcinogens by the International Agency for Research on Cancer Monographs.[1,2] These include Epstein-Barr virus (EBV), hepatitis B and C viruses (HBV and HCV, respectively), Kaposi sarcoma herpes virus (KSHV, also known as human herpes virus type 8, HHV-8), human immunodeficiency virus type 1 (HIV-1), human papillomavirus (HPV) type 16 (HPV-16), human T-cell lymphotropic virus type 1 (HTLV-1), *Helicobacter* (*H*) *pylori*, *Clonorchis* (C) *sinensis*, *Opisthorchis* (O) *viverrini*, and *Schistosoma* (*S*) *haematobium* (Table 1). The prevalence of these infectious agents and the burden of cancers attributable to infection are much higher in less developed regions of the world. Of the 12.7 million new cancer cases that occurred worldwide in 2008, about 2 million (16%) were attributable to infectious agents. This fraction was higher in less developed regions (22.9%) than in more developed regions (7.4%).[3]

INFECTIOUS AGENTS AND ASSOCIATED CANCERS

EBV can cause several types of cancer, including nasopharyngeal carcinoma (NPC), one of the most common cancers in South-Eastern Asia, and Burkitt lymphoma in children in Africa. Chronic infection with HBV and HCV is known to cause hepatocellular carcinoma (HCC). Chronic infection with HCV can also cause non-Hodgkin lymphoma (NHL), especially B-cell lymphoma. KSHV infection is associated with Kaposi sarcoma and primary effusion lymphoma, a rare subgroup of B-cell NHL. HIV-1 infection confers a high risk for cancer and leads to increased replication of oncogenic viruses such as EBV and KSHV, mainly through immune suppression. Infection with high-risk HPV types (i.e., HPV16, 18, 31, 33, 35, 39, 45, 51,

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From the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (J-KO, EW); The Risk Appraisal and Prevention Branch, National Cancer Control Institute, National Cancer Center, Goyang, Republic of Korea (J-KO); Cancer Registry of Norway, Oslo, Norway, Department of Genetic Epidemiology, Folkhälsan Research Center, Helsinki, Finland, and Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway (EW). Address correspondence to E.W.; e-mail: elisabete.weiderpass.vainio@ki.se

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Table 1. Infectious Agents, Associated Cancer Sites, and Mechanisms of Carcinogenesis[2]

Group 1 Infectious Agents	Cancer Sites	Mechanisms of Carcinogenesis
Epstein-Barr virus	Nasopharyngeal carcinoma, Burkitt lymphoma, immune-suppression-related non-Hodgkin lymphoma, extranodal natural killer/T-cell lymphoma (nasal type), Hodgkin lymphoma	Direct carcinogens
Hepatitis B virus	Hepatocellular carcinoma	Indirect carcinogens that act via chronic inflammation
Hepatitis C virus	Hepatocellular carcinoma, non-Hodgkin lymphoma	Indirect carcinogens that act via chronic inflammation
Kaposi sarcoma herpes virus	Kaposi sarcoma, primary effusion lymphoma	Direct carcinogens
Human immunodeficiency virus type 1	Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, carcinoma of the cervix, anus, conjunctiva	Indirect carcinogens that act via immune suppression
Human papillomavirus type 16	Carcinoma of the cervix, vulva, vagina, penis, anus, oral cavity, and oropharynx and tonsil	Direct carcinogens
Human T-cell lymphotropic virus type 1	Adult T-cell leukemia and lymphoma	Direct carcinogens
Helicobacter pylori	Non-cardia gastric carcinoma, low-grade B-cell MALT gastric lymphoma	Indirect carcinogens that act via chronic inflammation
Clonorchis sinensis	Cholangiocarcinoma	Indirect carcinogens that act via chronic inflammation
Opisthorchis viverrini	Cholangiocarcinoma	Indirect carcinogens that act via chronic inflammation
Schistosoma haematobium	Urinary bladder cancer	Indirect carcinogens that act via chronic inflammation

MALT, mucosa-associated lymphoid tissue.

52, 56, 58, and 59) can cause cervical carcinoma. HPV16 also can cause carcinoma of the vulva, vagina, penis, anus, oral cavity, oropharynx, and tonsil. HLTV-1 causes adult T-cell leukemia and lymphoma (ATLL). *H pylori* infection is associated with gastric carcinoma. *H pylori* infection also causes B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma. *C sinensis* and *O viverrini* are liver flukes that are endemic in North-Eastern Thailand and many areas of South-Eastern Asia, respectively. Infection with these parasites is associated with cholangiocarcinoma (CCA). *S haematobium* is endemic in most countries in Africa and the Eastern Mediterranean region, and infection with this parasite can cause urinary bladder cancer.

More recently, markel cell polyomavirus (MCPyV), a novel member of the polyomavirus family, has been identified.[4] There is some evidence that MCPyV has an important role in the development of Merkel cell carcinoma, a rare skin cancer arising in the elderly and chronically immunosuppressed individuals.[5]

GLOBAL BURDEN OF CANCERS ATTRIBUTABLE TO INFECTION

The number of cancers attributable to infection is dependent on the number of cancer cases and population attributable fractions, which show wide variation from 100% in cervical carcinoma to 2.3% in urinary bladder cancer.[3] As shown in Figure 1, a large majority of the global burden of cancers attributable to infection occurs in less developed regions.

The estimated number of new cases of and deaths from NPC worldwide in 2012 was 86,691 and 50,828, respectively. NPC is actually more prevalent in less developed regions than more developed regions. Indeed, 92% of NPC cases occur in less developed regions. High-risk regions include South-Eastern Asia (age-standardized rate [ASR], 4.3), Micronesia (ASR, 2.7), and Eastern Asia (ASR, 6).

NHL (385,741 new cases worldwide in 2012) and Hodgkin lymphoma (65,950 new cases worldwide in 2012) are more prevalent in more developed regions. High-risk regions for NHL include Northern America (ASR, 12.3), Australia/New Zealand (ASR, 12.1), Northern Europe (ASR, 9.7), Western Europe (ASR, 9.2), and Southern Europe (ASR, 8.4). High-risk regions for Hodgkin lymphoma include Northern America (ASR, 2.4), Western Europe (ASR, 2.4), Australia/New Zealand (ASR, 2.4), Southern Europe (ASR, 2.3), and Northern Europe (ASR, 2.2).[6] Differences in early detection and diagnosis between more and less developed regions[7] and competing causes of

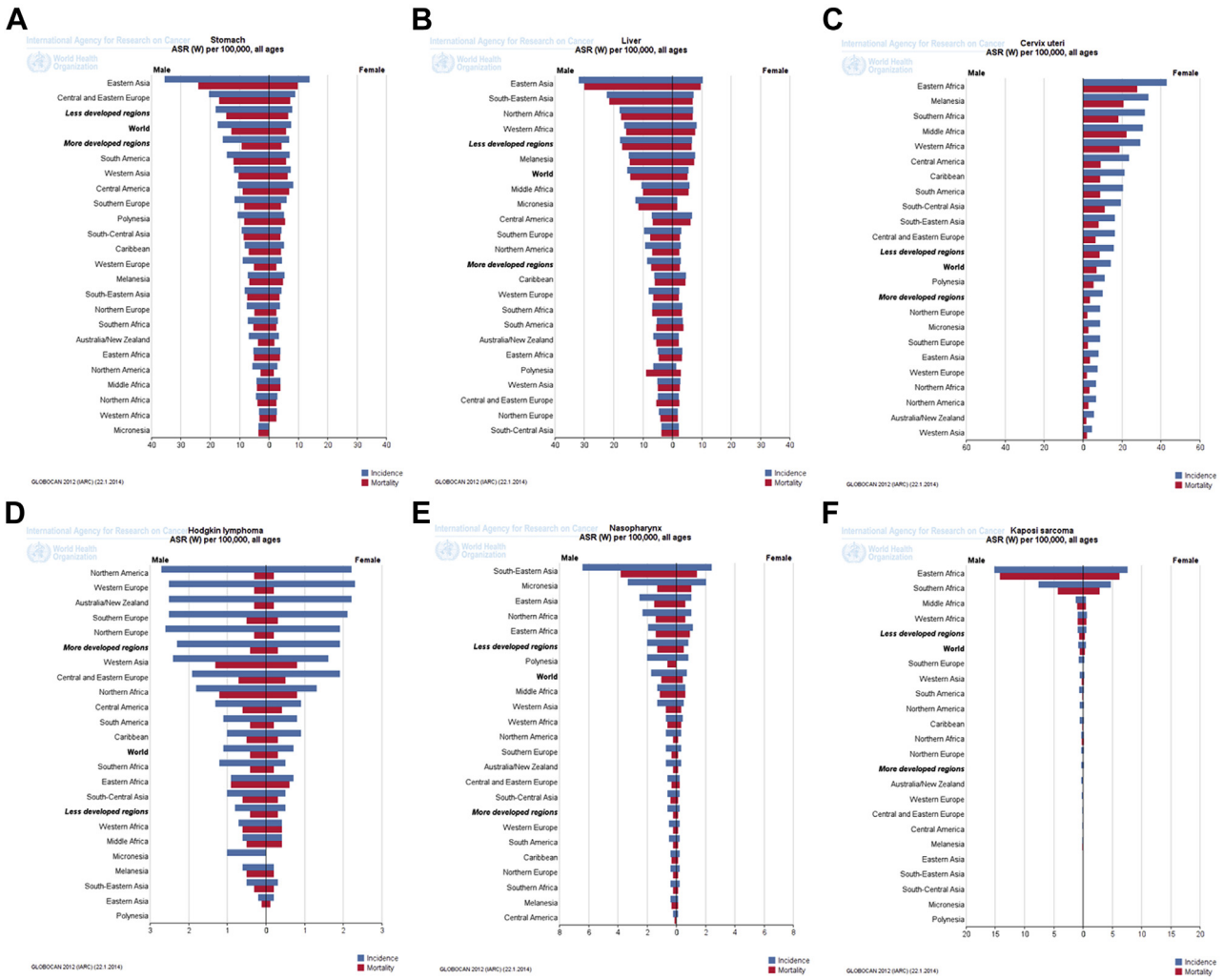

Figure 1. Geographical distribution of the incidence of selected cancers in 2012: estimated age-standardized rate (ASR). (A) stomach cancer, (B) liver cancer, (C) cervical cancer, (D) Hodgkin lymphoma, (E) nasopharyngeal carcinoma, and (F) Kaposi sarcoma.[6]

mortality may partially contribute to the geographic variation in the incidence of lymphoma. Moreover, patients with severe immunodeficiency who are at high risk for lymphoma in less developed regions tend to die of infectious diseases before lymphoma can develop.[8]

Liver cancer can also be defined as largely a problem of less developed regions. Indeed, 83% (50% in China alone) of the estimated 782,000 new cases worldwide occurred in less developed regions in 2012. In the same year, liver cancer was the fifth most common cancer in men (554,000 cases) and the ninth most common cancer in women (228,000 cases). In men, the regions of high incidence are Eastern Asia and South-Eastern Asia (ASRs, 31.9 and 22.2/100,000 men, respectively). In women, the rates are generally much lower, but are highest in Eastern Asia and Western Africa (ASRs, 10.2 and 8.1/100,000 women, respectively). Liver cancer is the second most common cause of cancer death worldwide, estimated to be responsible for nearly 746,000 deaths in 2012.[6]

Kaposi sarcoma is a relatively rare cancer with an estimated 44,247 new cases and 26,974 deaths worldwide in 2012. The majority of cases (85%) occur in Africa.[6]

Cervical carcinoma is the fourth most common cancer in women, with an estimated 528,000 new cases and 266,000 deaths worldwide in 2012. As with liver cancer, a large majority (>80%) of the global burden occurs in less developed regions, where cervical carcinoma accounts for almost 12% and 7.5% of all female cancer cases and deaths, respectively. High-risk regions include Eastern Africa (ASR, 42.7/100,000 women), Melanesia (33.3), Southern Africa (31.5) and Middle Africa (30.6).[6]

Gastric carcinoma is the fifth most common cancer in the world, after cancers of the lung, breast, and prostate, and colorectal cancer, with an estimated 952,000 new cases and 723,000 deaths in 2012. Of these new cases, more than 70% occurred in less developed regions (456,000 cases in men, 221,000 cases in women) and 50% occurred in Eastern Asia (mainly in China).[6]

CCA is relatively rare, but high incidence rates have been reported in Eastern Asia, especially in Thailand. Very high incidence rates (85/100,000) have been reported in northeast Thailand, where CCA represents approximately 85% of total primitive liver cancers,[9] and in other Asian countries such as China and Korea.[10]

Urinary bladder cancer is the sixth most common cancer in men with an estimated 330,380 new cases worldwide in 2012. The regions of high incidence in men include Southern Europe (ASR, 21.8), Western Europe (ASR, 19.7), Northern America (ASR, 19.5), Western Asia (ASR, 19), and Northern Africa (ASR, 15.1). In women, the rates are generally much lower (99,413 new cases), with the highest rates found in Northern America (ASR, 5.1), Western Europe (ASR, 4.3), Southern Europe (ASR, 3.8), Northern Europe (ASR, 3.6), and Northern Africa (ASR, 3.2).[6]

EPIDEMIOLOGY AND PATHOGENESIS

Epstein-Barr Virus

EBV infection is common and has been detected in populations throughout the world. In less developed regions, EBV infection tends to occur in children aged 3 or 4 years, whereas it is delayed until adolescence in more developed regions.[11] NPC is a highly invasive malignancy that is rare in most Western countries, but high incidence rates have been observed in certain populations in South-Eastern Asia and Northern Africa, especially in Southern China, Singapore, and Malaysia.[11] More than 95% of NPCs are undifferentiated (type II), and in high-incidence areas, nearly all cases are EBV-related.[3] The EBV latent membrane proteins 1 and 2 have profound effects on cellular gene expression and cellular growth and result in NPC. In addition to potential genetic changes, the establishment of a latent, transforming infection in epithelial cells is likely to be a major contributing factor to the development of this cancer.[12]

EBV infection is associated with several tumors of lymphoid tissues. In less developed regions, EBV is found in 90% of childhood Hodgkin lymphoma and 60% of Hodgkin lymphomas that occur in adulthood, whereas in more developed regions it is found in only 40% of cases.[2] The association between EBV infection and Burkitt lymphoma, which is primarily a childhood malignancy, has long been established. Endemic areas of Burkitt lymphoma are found in Papua New Guinea and sub-Saharan Africa, where in certain areas it is the most common childhood cancer.[11] In endemic areas, more than 95% of Burkitt lymphoma is attributable to EBV.[3] Although the precise etiologic role of EBV in the lymphomagenesis of Burkitt lymphoma remains unclear, EBV infection induces *c-myc* overexpression and cytogenetic changes that are sufficient to develop this disease.[13]

EBV is also associated with certain types of natural killer (NK)/T-cell lymphomas including extranodal NK/T-cell lymphoma of the nasal type, and there is growing evidence that EBV may be involved in the development of gastric carcinoma. Indeed, EBV is detected in 10% of gastric carcinomas worldwide.[14]

Hepatitis B Virus

HBV is transmitted by percutaneous and permucosal exposure to infected blood and other body fluids, including semen and vaginal fluid. Common modes of transmission include mother-to-infant, child-to-child, unsafe injection practices and blood transfusions, and sexual contact.[2]

There is large variation in the prevalence of HBV infection worldwide. The prevalence of chronic infection with HBV is low (<2% hepatitis B surface antigen [HBsAg]-positive) in Northern America, Northern Europe, Western Europe, and Australia/New Zealand; intermediate (2%-7% HBsAg-positive) in Japan, the Middle East, Eastern Europe, Southern Europe, and parts of South America; and high (>8% HBsAg-positive) in sub-Saharan Africa, the Amazon Basin, China, Korea, Taiwan, and several other countries in South-Eastern Asia.[15,16] From 1990 to 2005, the prevalence of chronic infection with HBV decreased in most regions. This was particularly evident in Central sub-Saharan Africa, Tropical and Central Latin America, South-Eastern Asia, and Central Europe. Despite this decrease in prevalence, the absolute number of HBsAg-positive individuals increased from 223 million in 1990 to 240 million in 2005. Strong declines were seen in children in South-Eastern Asia following the implementation of HBV vaccination programs.[17]

Chronic infection with HBV is associated with an increased risk for HCC. In a meta-analysis that included 37 case-control studies and 10 cohort studies, the odds ratio for HCC was estimated to be 13.5 for individuals with HBV infection compared with those without HBV infection.[18] HBV is a non-cytopathic virus and the hepatic inflammation and injury that occur in acute and chronic hepatitis and cirrhosis are attributed to host immune response. The underlying chronic necroinflammatory hepatic disease frequently provides a mitogenic, and possibly also a mutagenic environment in which virus-induced genetic changes can lead to hepatocarcinogenesis.[19,20] HBV may play a direct role in HCC via 2 major mechanisms: (a) the integration and mutation of the viral genome into the host cellular DNA, which may result in the altered expression of important cellular genes; or (b) the expression of HBV proteins, which may have a direct effect on cellular function and promote malignant transformation.[21]

Hepatitis C Virus

HCV can be transmitted by transfusion of blood and blood products, transplantation of solid organs from infected donors, injection drug abuse, unsafe therapeutic injections, and occupational exposure to blood.[22]

Globally, the prevalence of HCV infection increased from 2.3% to 2.8% between 1990 and 2005, with a corresponding increase in the number of individuals

positive for antibodies against HCV (from >122 million to >185 million). Central Asia, Eastern Asia, and Northern Africa/Middle East are estimated to have a high prevalence of HCV (>3.5%); South Asia, South-Eastern Asia, sub-Saharan Africa, Andean, Central, and Southern Latin America, Caribbean, Oceania, Australasia, and Central Europe, Eastern Europe, and Western Europe have a moderate prevalence (1.5%-3.5%); whereas the Asia Pacific, Tropical Latin America, and Northern America have low prevalence (<1.5%).[23] Chronic infection with HCV is one of the major risk factors for HCC. In a meta-analysis with 37 case-control studies and 4 cohort studies, the odds ratio for HCC was estimated to be 12.2 for individuals with HCV infection compared with those without the infection.[18]

The mechanisms underlying the progression of HCV infection to HCC are currently not fully understood. What is known is that most individuals with HCV infection fail to clear the virus. The infection then becomes persistent, leaving these individuals at long-term risk for progressive hepatic fibrosis, cirrhosis, or HCC. HCV has an exclusively cytoplasmic life cycle;[24,25] therefore HCV replication and potentially pro-oncogenic events are restricted to the cytoplasm. Although HCV infection leads to chronic inflammation, steatosis, fibrosis, and oxidative chromosomal DNA damage, several HCV proteins, such as the core protein, E1/E2 glycoproteins, p7, NS2, NS3, NS4, and NS5, have been shown to have direct oncogenic effects and to up-regulate mitogenic processes.[26,27]

Kaposi Sarcoma Herpes Virus

KSHV, also known as HHV-8, is a causal factor for Kaposi sarcoma, and also is associated with primary effusion lymphoma and some cases of multicentric Castleman disease.[2] KSHV is transmitted primarily via saliva. In countries where KSHV is highly prevalent, infection usually occurs during childhood and prevalence increases with age.[28-30] The peak age of transmission is generally between 6 and 10 years[30,31] and the risk for infection is increased if family members, especially mothers, are infected.[28,29,32,33] Other risk factors, especially HIV-1, play an important contributory role in the development of cancer.[29,33] In the United States, Europe, and Australia, the prevalence of KSHV is elevated in homosexual men, especially HIV-1-positive homosexual men.[34-36] In some areas of Europe and Northern America, after years of dramatically increasing incidence, a rapid decline in the incidence of Kaposi sarcoma followed the introduction of highly active antiretroviral therapy.[37] However, with the rapid spread of the HIV/AIDS epidemic in sub-Saharan Africa and the limited access to treatment, the estimated incidence of Kaposi sarcoma is around 40 per 100,000 person-years in Zimbabwe, making Kaposi sarcoma the most common cancer in men in that country.[38] The expert working group at the International Agency for Research on Cancer reviewed 22 cohort and 80 case-control studies, most of which reported relative risks for the association between KSHV infection and Kaposi sarcoma that were greater than 10.[2]

Primary effusion lymphoma is a very rare subgroup of B-cell NHL, which presents as pleural, peritoneal, and pericardial lymphomatous effusions. These comprise less than 2% of HIV-1-related lymphomas. There is already strong evidence that KSHV is a causal agent of primary effusion lymphoma.[2]

KSHV is able to increase the life span of infected cells. Primary infection induces features that are commonly seen in transformed cells, such activation of prosurvival signalling pathways.[39-41] These functions are carried out by multiple viral proteins acting in concert. Individual viral genes and microRNAs augment proliferation in multiple experimental systems and also modulate autophagy and oncogene-induced senescence.[42-45] To ensure continued cell survival, KSHV infection also modulates cellular immunity.[46-48]

HUMAN IMMUNODEFICIENCY VIRUS TYPE 1

HIV-1 is transmitted by 3 main routes: sexual intercourse, blood contact, and from mother to infant. Globally, an estimated 35.3 million people were living with HIV (HIV-1 and HIV-2) in 2012. Another 2.3 million people had new HIV infections, which was a 33% decline from the 2001 incidence of 3.4 million. About 95% of new HIV infections occur in less developed regions. In 2012, the prevalence of HIV ranged from less than 0.5% in more developed regions to up to 26% in some countries in sub-Saharan Africa in 2012.[49]

The 3 most common cancers in HIV-1-infected individuals are Kaposi sarcoma (caused by KSHV), lymphomas (many EBV-positive), and cervical and anogenital carcinomas associated with HPV infection.[2] These infectious etiologies explain why the associated cancers are greatly increased in immunosuppressed individuals. Indeed, infection with oncogenic viruses is much more common than the diseases these viruses cause, and the incidence and severity of these cancers is greatly increased by immunosuppression. Viruses have evolved to survive through 3 essential properties: transmission, lytic replication, and latency. Immune dysregulation may facilitate the development of cancer.[2]

HUMAN PAPILLOMAVIRUS

HPV infection is a necessary cause of cervical carcinoma. HPV DNA is found in almost 100% of samples of cervical carcinoma and cervical intraepithelial neoplasia grade 3 worldwide.[50-52] There are more than 100 different HPV types, about 40 of which are known to infect the genital tract and 12 of which are classified as group 1 carcinogens: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.[1,53]

HPV is transmitted mainly through direct skin-to-skin or skin-to-mucosa contact. Lifetime number of sexual partners has been shown to be the main determinant of anogenital HPV infection in both women and men.[54] In a meta-analysis that included 194 studies comprising 1 million women with normal cytologic results, the estimated global prevalence of HPV was 11.7%. Sub-Saharan Africa (24%), Eastern Europe (21.4%), and Latin America (16.1%) showed the highest prevalence.[55] HPV16 is also associated with carcinomas of the vulva, vagina, penis, anus, oral cavity, and oropharynx and tonsil.[1]

The HPV oncoproteins E6, E7, and E5 play an important role in regulating viral function during the viral life cycle and also contribute to the development of cancer. E6 and E7 promote cellular proliferation, prolong cell cycle progression, and prevent apoptosis.[56] p53 for E6 and retinoblastoma proteins for E7 have a crucial role in protecting genomic integrity by forcing apoptosis or inducing cell cycle arrest until errors in DNA replication can be repaired.[57-59]

HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE 1

HTLV-1 can be transmitted via sexual intercourse, from mother to child through breastfeeding, and via transfusion of infected blood products or sharing of needles and syringes.[60] HTLV-1 is endemic in certain areas, especially Southwestern Japan, the Caribbean, and parts of Africa and South America where up to 10% or more of the population may be infected.[61]

Adult T-cell leukemia/lymphoma occurs almost exclusively in areas where HTLV-1 infection is endemic. The cumulative incidence of ATLL among HTLV-1 carriers is estimated to be 1% to 5% in endemic areas.[62] Evidence of HTLV-1 infection was initially found in at least 90% of ATLL cases, and HTLV-1 infection subsequently became part of the diagnostic criteria for ATLL.[2] ATLL occurs mostly in adults, at least 20 to 30 years after the onset of HTLV-1 infection; individuals infected during childhood may be at higher risk for developing ATLL.[63] Screening of blood donors has been shown to be an effective strategy in preventing HTLV-1 transmission, and many countries in endemic areas have implemented systematic screening of all blood donors.[61]

Multiple factors, such as viral genes, genetic and epigenetic alterations, and the host immune system, may be implicated in the leukemogenesis of ATLL. Among them, the viral proteins tax and HBZ are thought to play important roles.[64] These proteins not only control viral gene transcription, but also modulate the proliferation of infected cells. The fact that HTLV-1 induces the proliferation of infected cells facilitates its transmission through cell-to-cell contact rather than through the release of viral particles.[2]

Helicobacter pylori

The prevalence of *H pylori* infection varies widely by geographic area, age, race, and socioeconomic status. In more developed regions, most infections occur in early childhood. The prevalence of *H pylori* in less developed regions may reach 70% or more compared with 40% or less in more developed regions.[65] *H pylori* infection is limited to the distal part of the stomach, and chronic infection with *H pylori* is typically associated with noncardia gastric carcinoma. Seventy-five percent of noncardia gastric carcinomas worldwide are attributable to *H pylori* (3), and *H pylori* is also associated with low-grade B-cell MALT gastric lymphoma (2).

The adhesion of *H pylori* to epithelial cells induces an inflammatory response, resulting in the recruitment of neutrophils, followed by B and T lymphocytes, macrophages, and plasma cells. Consequently, large amounts of reactive oxygen or nitrogen species, involved in epithelial cell damage and carcinogenesis, are generated.[66] The genomes of *H pylori* are highly diverse, and therefore bacterial virulence factors (e.g., cytotoxin-associated gene pathogenicity island-encoded virulence factors) play an important role in determining the outcome of *H pylori* infection, in combination with host responses that are augmented by environmental and dietary risk factors.[67]

Helminth Infections

C sinensis and *O viverrini* infections are caused primarily by the ingestion of raw (dried, pickled, or salted), or undercooked infected fish.[2] Chronic infections with these liver flukes are associated with CCA. Endemic areas are found in China, Korea, Thailand, Laos, Vietnam, and Cambodia. The relative risk for CCA is estimated to be 7.8 for individuals infected with *O viverrini* and 7.7 for individuals infected with *C sinensis*.[2] Thailand is the most endemic country for *O viverrini*, with an overall prevalence that decreased from 14% in 1980-1981 to 9.6% in 2001.[68] The incidence of CCA in the region with the highest prevalence of *O viverrini* in Thailand was more than 40 times greater than that in any other geographic region.[69] Around 5% to 10% of CAC is caused by chronic *C sinensis* infection in endemic areas.[70,71]

Infected intra- or extrahepatic bile ducts undergo severe pathological changes. Liver fluke antigens stimulate both inflammatory and hyperplastic changes in the bile ducts. The liver fluke excretes or secretes metabolic products, some of which are highly immunogenic, from the tegument and excretory openings into the bile.[72-74] The metabolic products themselves may be toxic to or interact with the biliary epithelium.[75]

S haematobium is associated with bladder cancer. Endemic areas are found in sub-Saharan Africa, the Sudan, Egypt, and Yemen.[2] The overall prevalence of *S haematobium* infection in Egypt is 37% to 48% and urinary bladder cancer accounts for about 31% of the total cancer incidence in Egypt; it is the most common type of cancer in men and the second most prevalent, after breast cancer, in women.[69] All *S haematobium*

infections follow direct contact with freshwater-harboring cercariae.[2]

S haematobium eggs induce chronic inflammation and irritation in the urinary bladder that seem to be associated with increased malignant transformation at the site of inflammation.[76] The inflammatory response around the eggs gives rise to genotoxic factors and products that may cause genomic instability in host cells, leading to modifications in the regulation of tumor suppressor genes and oncogenes, as well as stimulating a proliferative response in the host cells to repair tissue damage caused by the inflammation.[77,78]

BURDEN OF CANCERS ATTRIBUTABLE TO INFECTIONS

It has been estimated that 15.6% (1,450,000 cases) of the worldwide incidence of cancer in 1990 could be attributed to infection with either EBV, HBV and HCV, HIV-1, HPV, HTLV-1, *H pylori*, liver flukes or *Schistosomes*. There would have been 21% fewer cancer cases in less developed regions (1 million fewer cases per year) and 9% fewer cases in more developed regions (375,000 fewer cases per year) if these infectious diseases had been prevented. The attributable fraction at specific cancer sites varied from 89% of cervical carcinoma attributable to HPV to 1% of all leukemias attributable to HTLV-1.[79]

According to another study, there were an estimated 1.9 million cases of infection-attributable cancer in 2002, representing 17.8% of the global burden of cancer. The principal infectious agents were *H pylori* (5.5% of all cancer), HPV (5.2%), HBV and HCV (4.9%), EBV (1%), and HIV together with KSHV (0.9%). Relatively less important causes of cancer were the *Schistosomes* (0.1%), HTLV-1 (0.03%), and the liver flukes (0.02%). If these infections had been prevented, there would have been 26.3% fewer cancers in less developed regions (1.5 million cases per year) and 7.7% in more developed regions (390,000 cases). The attributable fraction at the specific cancer sites varied from 100% of cervical carcinoma attributable to HPV to a tiny proportion (0.4%) of HCC (worldwide) caused by liver flukes.[80]

A recent study showed that of the 12.7 million new cancer cases that occurred worldwide in 2008, the population attributable fraction for infectious agents was 16.1%, meaning that around 2 million new cancer cases were attributable to infectious agents.[3] This fraction was higher in less developed regions (22.9%) than in more developed regions (7.4%), and varied from 3.3% in Australia/New Zealand to 32.7% in sub-Saharan Africa. *H pylori*, HBV and HCV, and HPV were responsible for 1.9 million cases, mainly gastric carcinoma, HCC, and cervical carcinoma. In women, cervical carcinoma accounted for about half of the infection-related burden of cancer; in men, HCC and gastric carcinoma accounted for more than 80%. In the recent study, around 30% of cancers attributable to infections occurred in people younger than 50 years of age.[3]

ROLE OF TREATMENT OF INFECTION ON CANCER RISK

The primary treatment goals for patients with HBV and HCV infection are to prevent progression of the infection, particularly to cirrhosis and HCC. Approved and widely used treatments include conventional interferon (IFN)-α and pegylated (PEG) IFN-α-2a; the nucleoside analogs lamivudine, entecavir, and telbivudine; and the nucleotide analog adefovir dipivoxil and tenofovir.[81] A combination of PEG IFN-α and ribavirin has been widely used for the treatment of chronic infection with HCV. Two NS3-4A protease inhibitors, telaprevir and boceprevir, have been approved in combination with pegylated IFN-α and ribavirin for the treatment of chronic infection with HCV genotype 1.[82]

Antiviral treatments for HPV, EBV, KSHV, and HTLV-1 have had limited success in treating cervical carcinoma, EBV-associated lymphoma and post-transplant lymphoproliferative disorder, KSHV-associated Kaposi sarcoma in AIDS patients, and HTLV-1-associated acute, chronic, and smoldering subtypes of adult T-cell lymphoma, respectively.

A combination of various antibiotics has been used to eradicate *H pylori*. These antibiotics are often used in combination with antisecretory agents, such as proton pump inhibitors, or with bismuth salts. Guidelines for the management of *H pylori* infection have been proposed for the Asia Pacific region,[83] less developed regions,[84] Europe,[85] and the United States.[86] Testing and treatment for *H pylori* is indicated in patients with diseases such as active peptic ulcer disease and gastric MALT lymphoma. Despite evidence that *H pylori* eradication is effective for the prevention of gastric carcinoma,[87,88] screening and treatment of *H pylori* in the general population have not yet been recommended in light of the possible harms, including antibiotic resistance.[89]

Praziquantel is the major chemotherapeutic agent used to treat *C sinensis*, *O viverrini*, and *S haematobium* infections. However, tribendimidine also has recently been found effective, and is now under investigation as a promising chemotherapeutic alternative.[90-92]

PREVENTIVE METHODS

Widespread application of existing public health methods for the prevention of infections, such as vaccination (i.e., HBV and HPV vaccinations), safer injection practices, quality-assured screening of all donated blood and blood components, antimicrobial treatments, eating habits that avoid raw or undercooked fish consumption,

or safer sex practices, including condom use and minimizing one's lifetime number of sexual partners, could have a substantial effect on the future burden of cancer worldwide.

CONCLUSION

The global burden of cancer attributable to infection is substantial and less developed regions shoulder the majority of the burden. Carcinogenic biological agents have been identified, routes of transmission have been discovered, and we have methods to prevent and control infections. We can expect millions of lives to be saved due to HBV and HPV vaccination in the near future. Existing preventive methods other than vaccination can also help to decrease the future burden of cancer worldwide. Further studies and evaluation of other potential carcinogenic biological agents are needed.

References

1. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens—part B: biological agents. Lancet Oncol 2009;10:321–2.
2. International Agency for Research on Cancer. Monographs on the Evaluation of Carcinogenic Risks to Humans. A Review of Carcinogen—Part B: Biological Agents. Lyon, France: International Agency for Research on Cancer; 2011.
3. de Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol 2012;13:607–15.
4. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science 2008;319:1096–100.
5. Shuda M, Feng H, Kwun HJ, et al. T antigen mutations are a human tumor-specific signature for Merkel cell polyomavirus. Proc Natl Acad Sci U S A 2008;105:16272–7.
6. GLOBOCAN 2012 [Internet]. International Agency for Research on Cancer. 2013 [cited 07 January 2014]. Available from: http://globocan.iarc.fr/. Accessed October 3, 2014.
7. Rogena EA, De Falco G, Schurfeld K, Leoncini L. A review of the trends of lymphomas in the equatorial belt of Africa. Hematol Oncol 2011;29:111–5.
8. Dal Maso L, Serraino D, Franceschi S. Epidemiology of AIDS-related tumours in developed and developing countries. Eur J Cancer 2001;37:1188–201.
9. Poomphakwaen K, Promthet S, Kamsa-Ard S, et al. Risk factors for cholangiocarcinoma in Khon Kaen, Thailand: a nested case-control study. Asia Pac J Cancer Prev 2009;10:251–8.
10. Shin HR, Oh JK, Masuyer E, et al. Comparison of incidence of intrahepatic and extrahepatic cholangiocarcinoma—focus on East and South-Eastern Asia. Asia Pac J Cancer Prev 2010;11:1159–66.
11. Hjalgrim H, Friborg J, Melbye M. The epidemiology of EBV and its association with malignant disease. In: Arvin A, Campadelli-Fiume G, Mocarski E, et al., eds. Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis. Cambridge, UK: Cambridge University Press; 2007.
12. Raab-Traub N. Epstein-Barr virus in the pathogenesis of NPC. Semin Cancer Biol 2002;12:431–41.
13. Okano M, Gross TG. Acute or chronic life-threatening diseases associated with Epstein-Barr virus infection. Am J Med Sci 2012;343:483–9.
14. Chen JN, He D, Tang F, Shao CK. Epstein-Barr virus-associated gastric carcinoma: a newly defined entity. J Clin Gastroenterol 2012;46:262–71.
15. Chen CJ, Wang LY, Yu MW. Epidemiology of hepatitis B virus infection in the Asia-Pacific region. J Gastroenterol Hepatol 2000;15(Suppl):E3–6.
16. Custer B, Sullivan SD, Hazlet TK, Iloeje U, Veenstra DL, Kowdley KV. Global epidemiology of hepatitis B virus. J Clin Gastroenterol 2004;38(Suppl 3):S158–68.
17. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine 2012;30:2212–9.
18. Cho LY, Yang JJ, Ko KP, et al. Coinfection of hepatitis B and C viruses and risk of hepatocellular carcinoma: systematic review and meta-analysis. Int J Cancer 2011;128:176–84.
19. Arbuthnot P, Kew M. Hepatitis B virus and hepatocellular carcinoma. Int J Exp Pathol 2001;82:77–100.
20. Chisari FV. Rous-Whipple Award Lecture. Viruses, immunity, and cancer: lessons from hepatitis B. Am J Pathol 2000;156:1117–32.
21. Brechot C, Kremsdorf D, Soussan P, et al. Hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC): molecular mechanisms and novel paradigms. Pathologie-biologie 2010;58:278–87.
22. Alter MJ. Epidemiology of hepatitis C virus infection. World J Gastroenterol 2007;13:2436–41.
23. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology 2013;57:1333–42.
24. Lindenbach BD, Pragai BM, Montserret R, et al. The C terminus of hepatitis C virus NS4A encodes an electrostatic switch that regulates NS5A hyperphosphorylation and viral replication. J Virol 2007;81:8905–18.
25. Moradpour D, Penin F, Rice CM. Replication of hepatitis C virus. Nat Rev Microbiol 2007;5:453–63.
26. Koike K. Pathogenesis of HCV-associated HCC: dual-pass carcinogenesis through activation of oxidative stress and intracellular signaling. Hepatol Res 2007;37(Suppl 2):S115–1120.
27. McGivern DR, Lemon SM. Tumor suppressors, chromosomal instability, and hepatitis C virus-associated liver cancer. Annu Rev Pathol 2009;4:399–415.
28. Dedicoat M, Newton R, Alkharsah KR, et al. Mother-to-child transmission of human herpesvirus-8 in South Africa. J Infect Dis 2004;190:1068–75.
29. Malope BI, Pfeiffer RM, Mbisa G, et al. Transmission of Kaposi sarcoma-associated herpesvirus between mothers and children in a South African population. J Acquir Immune Defic Syndr 2007;44:351–5.
30. Whitby D, Luppi M, Sabin C, et al. Detection of antibodies to human herpesvirus 8 in Italian children: evidence for horizontal transmission. Br J Cancer 2000;82:702–4.
31. Mbulaiteye SM, Pfeiffer RM, Engels EA, et al. Detection of kaposi sarcoma-associated herpesvirus DNA in saliva and buffy-coat samples from children with sickle cell disease in Uganda. J Infect Dis 2004;190:1382–6.
32. Plancoulaine S, Abel L, van Beveren M, et al. Human herpesvirus 8 transmission from mother to child and between siblings in an endemic population. Lancet 2000;356:1062–5.
33. Minhas V, Crabtree KL, Chao A, et al. Early childhood infection by human herpesvirus 8 in Zambia and the role of human immunodeficiency virus type 1 coinfection in a highly endemic area. Am J Epidemiol 2008;168:311–20.
34. Grulich AE, Cunningham P, Munier ML, et al. Sexual behaviour and human herpesvirus 8 infection in homosexual men in Australia. Sex Health 2005;2:13–8.
35. Martin JN, Ganem DE, Osmond DH, Page-Shafer KA, Macrae D, Kedes DH. Sexual transmission and the natural history of human herpesvirus 8 infection. N Engl J Med 1998;338:948–54.
36. Smith NA, Sabin CA, Gopal R, et al. Serologic evidence of human herpesvirus 8 transmission by homosexual but not heterosexual sex. J Infect Dis 1999;180:600–6.
37. Franceschi S, Lise M, Clifford GM, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. Br J Cancer 2010;103:416–22.
38. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Intl J Cancer 2010;127:2893–917.
39. Bhatt AP, Damania B. AKTivation of PI3K/AKT/mTOR signaling pathway by KSHV. Front Immunol 2012;3:401.
40. Chandran B. Early events in Kaposi's sarcoma-associated herpesvirus infection of target cells. J Virol 2010;84:2188–99.
41. Mesri EA, Cesarman E, Boshoff C. Kaposi's sarcoma and its associated herpesvirus. Nat Rev Cancer 2010;10:707–19.

42. Damania B, Cesarman E. Kaposi's sarcoma-associated herpesvirus. In: Knipe DM, Howley P, eds. Fields Virology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2013:2080–128.
43. Lee JS, Li Q, Lee JY, et al. FLIP-mediated autophagy regulation in cell death control. Nat Cell Biol 2009;11:1355–62.
44. Lei X, Bai Z, Ye F, et al. Regulation of NF-kappaB inhibitor Ikappa-Balpha and viral replication by a KSHV microRNA. Nat Cell Biol 2010;12:193–9.
45. Leidal AM, Cyr DP, Hill RJ, Lee PW, McCormick C. Subversion of autophagy by Kaposi's sarcoma-associated herpesvirus impairs oncogene-induced senescence. Cell Host Microbe 2012;11:167–80.
46. Bhatt AP, Jacobs SR, Freemerman AJ, et al. Dysregulation of fatty acid synthesis and glycolysis in non-Hodgkin lymphoma. Proc Natl Acad Sci U S A 2012;109):11818–23.
47. Delgado T, Carroll PA, Punjabi AS, Margineantu D, Hockenbery DM, Lagunoff M. Induction of the Warburg effect by Kaposi's sarcoma herpesvirus is required for the maintenance of latently infected endothelial cells. Proc Natl Acad Sci U S A 2010;107:10696–701.
48. Delgado T, Sanchez EL, Camarda R, Lagunoff M. Global metabolic profiling of infection by an oncogenic virus: KSHV induces and requires lipogenesis for survival of latent infection. PLoS Pathog 2012;8:e1002866.
49. The Joint United Nations Programme on HIV/AIDS (UNAIDS). Global Report: UNAIDS Report on the Global AIDS Epidemic 2013. Geneva, Switzerland: UNAIDS; 2013.
50. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189:12–9.
51. de Sanjose S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol 2010;11:1048–56.
52. Li N, Franceschi S, Howell-Jones R, Snijders PJ, Clifford GM. Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: variation by geographical region, histological type and year of publication. Intl J Cancer 2011;128:927–35.
53. de Villiers EM, Fauquet C, Broker TR, Bernard HU, zur Hausen H. Classification of papillomaviruses. Virology 2004;324:17–27.
54. Burchell AN, Winer RL, de Sanjose S, Franco EL. Epidemiology and transmission dynamics of genital HPV infection. Vaccine 2006;24(Suppl 3):S3/52–61.
55. Bruni L, Diaz M, Castellsague X, Ferrer E, Bosch FX, de Sanjose S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. J Infect Dis 2010;202:1789–99.
56. Ghittoni R, Accardi R, Hasan U, Gheit T, Sylla B, Tommasino M. The biological properties of E6 and E7 oncoproteins from human papillomaviruses. Virus Genes 2010;40:1–13.
57. Boyer SN, Wazer DE, Band V. E7 protein of human papilloma virus-16 induces degradation of retinoblastoma protein through the ubiquitin-proteasome pathway. Cancer Res 1996;56:4620–5624.
58. Munger K, Basile JR, Duensing S, et al. Biological activities and molecular targets of the human papillomavirus E7 oncoprotein. Oncogene 2001;20:7888–98.
59. Tommasino M, Accardi R, Caldeira S, et al. The role of TP53 in cervical carcinogenesis. Hum Mutat 2003;21:307–12.
60. Manns A, Hisada M, La Grenade L. Human T-lymphotropic virus type I infection. Lancet 1999;353:1951–8.
61. Proietti FA, Carneiro-Proietti AB, Catalan-Soares BC, Murphy EL. Global epidemiology of HTLV-I infection and associated diseases. Oncogene 2005;24:6058–68.
62. Murphy EL, Hanchard B, Figueroa JP, et al. Modelling the risk of adult T-cell leukemia/lymphoma in persons infected with human T-lymphotropic virus type I. Intl J Cancer 1989;43:250–3.
63. Pawson R, Schulz T, Matutes E, Catovsky D. Absence of HTLV-I/II in T-prolymphocytic leukaemia. Br J Haematol 1998;102:872–3.
64. Matsuoka M, Jeang KT. Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation. Nat Rev Cancer 2007;7:270–80.
65. Brown LM. Helicobacter pylori: epidemiology and routes of transmission. Epidemiol Rev 2000;22:283–97.
66. Correa P, Houghton J. Carcinogenesis of Helicobacter pylori. Gastroenterology 2007;133:659–72.
67. Wroblewski LE, Peek RM Jr. Helicobacter pylori in gastric carcinogenesis: mechanisms. Gastroenterol Clin North Am 2013;42:285–98.
68. Jongsuksuntigul P, Imsomboon T. Opisthorchiasis control in Thailand. Acta Trop 2003;88:229–32.
69. Fried B, Reddy A, Mayer D. Helminths in human carcinogenesis. Cancer Lett 2011;305:239–49.
70. Shin A, Park S, Shin HR, et al. Population attributable fraction of infection-related cancers in Korea. Ann Oncol 2011;22:1435–42.
71. Shin HR, Oh JK, Lim MK, et al. Descriptive epidemiology of cholangiocarcinoma and clonorchiasis in Korea. J Korean Med Sci 2010;25:1011–6.
72. Choi MH, Park IC, Li S, Hong ST. Excretory-secretory antigen is better than crude antigen for the serodiagnosis of clonorchiasis by ELISA. Korea J Parasitol 2003;41:35–9.
73. Sripa B, Kaewkes S. Localisation of parasite antigens and inflammatory responses in experimental opisthorchiasis. Intl J Parasitol 2000;30:735–40.
74. Wongratanacheewin S, Bunnag D, Vaeusorn N, Sirisinha S. Characterization of humoral immune response in the serum and bile of patients with opisthorchiasis and its application in immunodiagnosis. Am J Trop Med Hyg 1988;38(2):356–62.
75. Sripa B. Pathobiology of opisthorchiasis: an update. Acta Trop 2003;88:209–20.
76. Rosin MP. Saad el Din Zaki S, Ward AJ, Anwar WA. Involvement of inflammatory reactions and elevated cell proliferation in the development of bladder cancer in schistosomiasis patients. Mutat Res 1994;305:283–92.
77. Badawi AF. Molecular and genetic events in schistosomiasis-associated human bladder cancer: role of oncogenes and tumor suppressor genes. Cancer Lett 1996;105:123–38.
78. Rosin MP, Anwar WA, Ward AJ. Inflammation, chromosomal instability, and cancer: the schistosomiasis model. Cancer Res 1994;54(Suppl):1929s–33s.
79. Pisani P, Parkin DM, Munoz N, Ferlay J. Cancer and infection: estimates of the attributable fraction in 1990. Cancer Epidemiol Biomarkers Prev 1997;6:387–400.
80. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Intl J Cancer 2006;118:3030–44.
81. Liaw YF, Chu CM. Hepatitis B virus infection. Lancet 2009;373:582–92.
82. Pawlotsky JM. Treatment of chronic hepatitis C: current and future. Curr Top Microbiol Immunol 2013;369:321–42.
83. Fock KM, Katelaris P, Sugano K, et al. Second Asia-Pacific Consensus Guidelines for Helicobacter pylori infection. J Gastroenterol Hepatol 2009;24:1587–600.
84. Hunt RH, Xiao SD, Megraud F, et al. Helicobacter pylori in developing countries. World Gastroenterology Organisation Global Guideline. J Gastrointestin Liver Dis 2011;20:299–304.
85. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection–the Maastricht IV/ Florence Consensus Report. Gut 2012;61:646–64.
86. Chey WD, Wong BC. Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. Am J Gastroenterol 2007;102:1025–808.
87. Fukase K, Kato M, Kikuchi S, et al. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. Lancet 2008;372:392–7.
88. Ma JL, Zhang L, Brown LM, et al. Fifteen-year effects of Helicobacter pylori, garlic, and vitamin treatments on gastric cancer incidence and mortality. J Natl Cancer Inst 2012;104:488–92.
89. Park JY, Forman D, Greenberg ER, Herrero R. Helicobacter pylori eradication in the prevention of gastric cancer: are more trials needed? Curr Oncol Rep 2013;15:517–25.
90. Keiser J, Vargas M. Effect of artemether, artesunate, OZ78, praziquantel, and tribendimidine alone or in combination chemotherapy on the tegument of Clonorchis sinensis. Parasitol Intl 2010;59:472–6.
91. Soukhathammavong P, Odermatt P, Sayasone S, et al. Efficacy and safety of mefloquine, artesunate, mefloquine-artesunate, tribendimidine, and praziquantel in patients with Opisthorchis viverrini: a randomised, exploratory, open-label, phase 2 trial. Lancet Infect Dis 2011;11:110–8.
92. Xiao SH, Xue J, Xu LL, Zhang YN, Qiang HQ. Comparative effect of mebendazole, albendazole, tribendimidine, and praziquantel in treatment of rats infected with Clonorchis sinensis. Parasitol Res 2011;108:723–30.