REVIEW

Epidemiology of cancers of infectious origin and prevention strategies

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Key words

Cancer • Infectious diseases • Prevention

Summary

Infectious and parasitic diseases represent the third cause of cancer worldwide. A number of infectious and parasitic agents have been suspected or recognized to be associated with human cancers, including DNA viruses, such as papillomaviruses (several HPV types), herpesviruses (EBV and KSHV), polyomaviruses (SV40, MCV, BK, and JCV), and hepadnaviruses (HBV); RNA viruses, such as flaviviruses (HCV), defective viruses (HDV), and retroviruses (HTLV-I, HTLV-II, HIV-1, HIV-2,HERV-K, and XMRV); bacteria, such as H. pylori, S. typhi, S. bovis, Bartonella, and C. pneumoniae; protozoa, such as P. falciparum; trematodes, such as S. haematobium, S. japonicum, S. mansoni, O. viverrini, O. felineus, and C. sinensis. Each one of the chronic infections with H. pylori, HPV, and HBV/HCV is responsible for approximately the 5% of all human cancers. The primary prevention of infection-related cancers is addressed both to avoidance and eradication of chronic infections and to protection of the host organism. Vaccines provide fundamental tools for the prevention of infectious diseases and related cancers. The large-scale application of the HBV vaccine has already shown to favorably affect the epidemiological burden of primary hepatocellular carcinoma, and HPV vaccines have specifically been designed in order to prevent cervical cancer and other HPV-related cancers. The secondary prevention of infection-associated cancers has already found broad applications in the control of cervical cancer. Detection of early gastric cancer by endoscopy has been applied in Asian countries. Avoidance of local relapses, invasion, and metastasis may be achieved by applying tertiary prevention, which targets specific mechanisms, such as angiogenesis.

Epidemiology of infection-associated cancers

Global burden

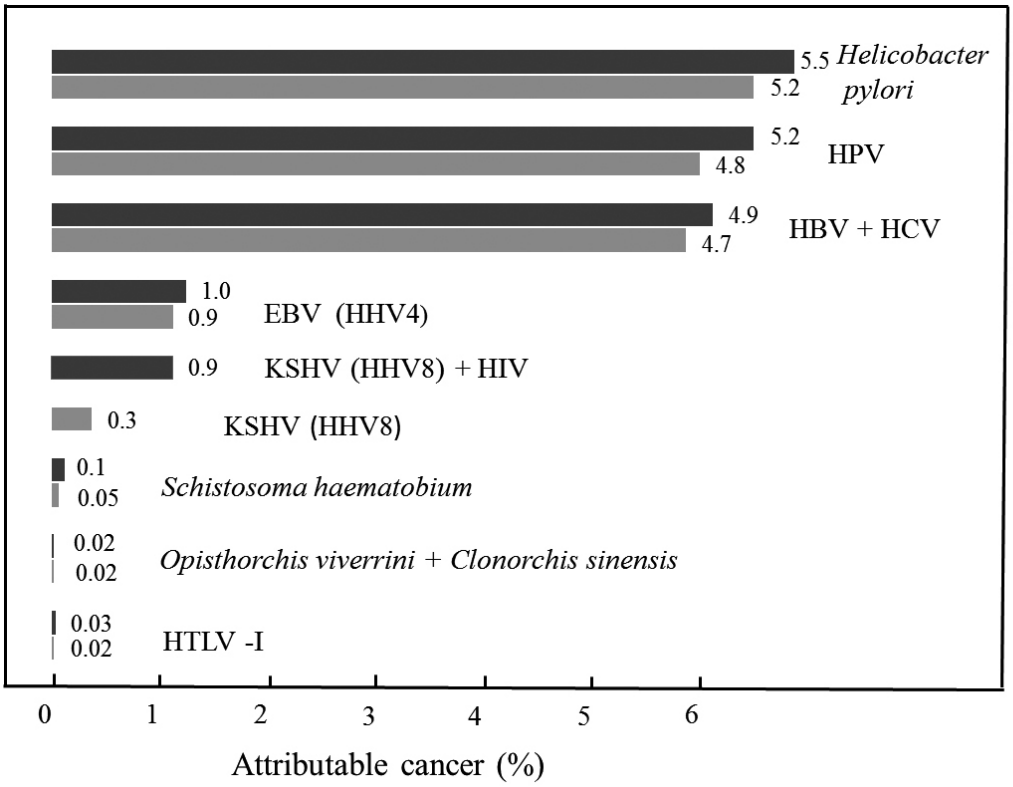
After dietary factors and tobacco smoke, infectious diseases represent the third leading cause of cancer worldwide. The population attributable fraction, which indicates the proportion of cancers associated with infectious and parasitic diseases, was estimated to be the 10% in the US population in 1981 [1], 10-20% in the UK population in 1998 [2], 3.6% in the French population in 2000 [3], 5% (range of acceptable estimates: 4-15%) in the UK population in 2005 [4], and 29.4% (31.7% in men and 25.3% in women) in the Chinese population in 2005 [5]. In the world population, it was estimated to be the 15.6% in 1990 [6], 17.8% in 2002 [7], and 16.1% in 2008 [8] . The last figure would correspond to about 2 million new cases of infection-related cancers diagnosed all over the world in 2008 [8].

The above estimates in the world population take into account the attributable fraction relative to the infections categorized in Group 1 by the International Agency for Research on Cancer (IARC), highlighting the infectious and parasitic agents for which there is sufficient evidence for carcinogenicity to humans [9]. Figure 1, which summarizes the results of two recent estimates [7, 8], shows, at a glance, the paramount importance of chronic infections in the etiology of cancer on a global scale. In particular, it appears that the chronic infections with *Helicobacter pylori*, human papillomaviruses (HPV), and hepatitis B (HBV) and C (HCV) viruses are each responsible for approximately the 5% of all human cancers and, altogether, they accounted for the 15.6% of human cancers worldwide in 2002 [7] and for the 14.7% in 2008 [8].

There are sharp differences in the epidemiological impact of infection-associated cancers between developing countries and developed countries, where the population attributable fraction has been estimated to be the 26.3% and 7.7% of cases, respectively [7] . These differences are due to geographical variations in the endemicity of infectious and parasitic agents associated with cancer as well as to the distinctive availability of preventive and therapeutic means towards both cancers and the related infectious diseases. Interestingly, lung cancer, colorectal cancers, breast cancer, and prostate cancer are, in terms of incidence, the 4 leading cancers in most geographical regions in the world [10]. The large majority of the exceptions to the above set of 4 cancers can be ascribed to cancers associated with infectious and parasitic diseases, which appear to contribute substantially to the disparities in cancer incidence between developed countries and developing countries.

A number of chronic viral, bacterial and protozoan infections and trematode infestations have been associated with human cancers affecting a variety of anatomical

Fig. 1. Fractions of cancers attributable to infectious agents categorized in IARC Group 1, as related to the total number of cancer cases in the world population in 2002 [7] (dark grey columns) and 2008 [8] (light grey columns).



sites. Table I reports a list of these agents, along with their categorization by IARC concerning the evidence of carcinogenicity to humans.

Viral infections

Among DNA viruses, a dozen of HPV types, including types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59, have been allocated by IARC in Group 1, as their carcinogenicity to humans has been sufficiently demonstrated. Other HPV types are categorized either in Group 2A (probably carcinogenic), Group 2B (possibly carcinogenic) or Group 3 (inadequate evidence of carcinogenicity to humans). The overall fraction of cancer attributable to HPV infection was estimated to be the 5.2% in 2002 [7] and the 4.8% in 2008 [8]. The persistent infection of the uterine cervix by HPV is responsible for virtually the 100% of cervical cancers, although other factors may interact with HPV in the etiology of cervical cancer, which is the third leading cancer in the world female population in terms of mortality. In addition, HPV can target other sites in the anogenital region of women and/or men (vulva, vagina, penis, and anus), in the upper aerodigestive tract (mouth and oropharynx), and in the skin.

Herpesviridae include two important cancer-associated viruses, both of which are categorized in IARC Group 1. Each of them has been associated with almost the 1% of all human cancers (Fig. 1). One is the Epstein-Barr virus (EBV), or human herpersvirus 4 (HHV4), which causes infectious mononucleosis during adolescence and young adulthood while it is associated, in certain geographical areas, with several types of lymphoma. The most important EBV-related cancer is Burkitt's lymphoma, which is a quite common childhood cancer in sub-Saharan Africa. The most likely interpretation for the distinctive pathogenic spectrum of EBV in different geographical areas is a possible association with malaria where the Burkitt's lymphoma is prevalent (see below). In addition to lymphomas, EBV is associated with nasopharyngeal carcinoma, presumably in connection with genetic factors. The other cancer-associated virus of this family is the Kaposi's sarcoma-associated herpesvirus (KHSV), or human herpesvirus 8 (HHV8), which has been discovered in patients affected by acquired immunodeficiency syndrome (AIDS).

Four viruses belonging to the family of *polyomaviridae*, including SV40, MCV, BK, and JCV, have been evaluated for their association with human cancers [11]. SV40 (simian virus 40) has been suspected to be associated with mesothelioma. While its carcinogenicity to humans appears to be inadequate, there is sufficient evidence for SV40 carcinogenicity in experimental animals, also in association with asbestos. Nevertheless, SV40 has been allocated by IARC in Group 3, indicating that this virus is not classifiable as to its carcinogenicity to humans. MCV (Merkel cell virus) has been associated with MCC (Merkel cell carcinoma). Being its carcinogenicity not supported by studies in experimental animals, it has been

Tab. I. Pathogenic agents suspected or recognized to be associated with human cancers, and their allocation in IARC Groups according to the evidence of carcinogenicity to humans.

Pathogenic agent[1]	IARC Group[2]
DNA viruses	
HPV, alpha types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59	1
HPV, alpha type 68	2A
HPV, alpha types 26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85 and 97,and beta types 5 and 8	2B
HPV, alpha types 6 and 11, other beta and gamma types	3
EBV (HHV4)	1
KSHV (HHV8)	1
SV40	3
MCV	2A
BKV	2B
JCV	2B
HBV	1
RNA viruses	
HCV	1
HDV	3
HTLV-I	1
HTLV-II	3
HIV-1	1
HIV-2	2B
HERV-K	NA
XMRV	NA
Bacteria	
Helicobacter pylori	1
Salmonella typhi	NA
Streptococcus bovis	NA
Bartonella species	NA
Chlamidophila pneumoniae	NA
Protozoa	
Plasmodium falciparum	2A
Trematodes	
Schistosoma haematobium	1
Schistosoma japonicum	2B
Schistosoma mansoni	3
Opistorchis viverrini	1
Opistorchis felineus	3
Chlonorchis sinensis	1

[1] See text for acronyms.

[2] Group 1, sufficient evidence of carcinogenicity to humans; Group 2A, probably carcinogenic; Group 2 B, possibly carcinogenic; Group 3, inadequate evidence of carcinogenicity to humans; NA, not available.

categorized as probably carcinogenic to humans (Group 2A). Two other polyomaviruses, BKV and JCV, were classified as possibly carcinogenic to humans (Group 2B) because the evidence for carcinogenicity to animals is sufficient, whereas their carcinogenicity to humans was evaluated to be inadequate. Both BK and JC are the initials of the patients from whom the viruses were isolated for the first time. In particular, BKV was found to induce a broad variety of tumors, also depending on the administration route, in hamsters, rats, and mice, but human data for prostate cancer and other types of cancer are inconsistent. Likewise, brain tumors were induced in monkeys and hamsters injected intracerebrally with JVC, but there is no clear association between JCV infection in humans and cancers [11].

HBV and HCV are hepatotropic viruses whose infection may evolve into chronic viral hepatitis. They are quite different viruses, being HBV a DNA virus belonging to the family of *hepadnaviridae*, whereas HCV is an RNA virus belonging to the family of *flaviviridae*. Both viruses are allocated in IARC Group 1 and, collectively, they were estimated to be responsible for the 4.9% of cancers in the world population in 2002 [7] and for the 4.7% in 2008 [8]. They have been associated with the 85.5% of cases of hepatocellular carcinomas (HCC), the 54.4% of which is attributable to HBV and the 31.1% is attributable to HCV [7]. The HBV nucleocapsid encloses the circular viral DNA, which is not fully double-stranded, and a DNA polymerase that has reverse transcriptase activity. A variety of mechanisms, spanning from integration of HBV DNA into the cellular genome to induction of cellular oncogenes by HBV gene products (e.g., HBx-Ag), deletion or mutation of tumor suppressor genes, and liver cirrhosis with inflammation, necrosis and regeneration , have been proposed as mechanisms involved in HBV carcinogenesis. Our studies have highlighted the importance of synergisms with chemical hepatocarcinogens (e.g., aflatoxin B1 and food pyrolysis products), whose metabolic activation is enhanced in the liver both of humans infected with HBV and of woodchucks infected with WHV (woodchuck hepatitis virus), which shares similarities with HBV [12-15]. The hepatitis D virus (HDV), or hepatitis delta antigen, having a circular RNA genome and needing the surface antigen of HBV (HBsAg) to establish infection in humans either as a co-infection or a superinfection, was classified in Group 3 by IARC several years ago [16], as the demonstration of HDV contribution to HCC induction by HBV was not adequate. However, more recently it has been suggested that the risk of hepatocellular carcinoma is higher when HBV is superinfected with HDV [17].

The RNA strands of *retroviruses* are complexed with reverse transcriptase and are thus transcribed into a double-stranded DNA that is inserted into the host genome, an obligatory step for their replication [18]. HTLV-I (human T-cell lymphotropic virus type 1) has been associated with adult T cell leukemia/lymphoma and it is allocated in IARC Group 1, whereas HTLV-II is in Group 3. HIV-1 (human immunodeficiency virus type 1) is the etiological agent of AIDS (acquired immune deficiency syndrome), which, due to immunodeficiency, has been associated with several human cancers and especially with KHSV-related Kaposi's sarcoma and non-Hodgkin's lymphoma. HIV-2 is possibly carcinogenic to humans. Two other retroviruses have been suspected to be associated with human cancers. One is HERV-K (hu-

man endogenous retrovirus), which may be involved in breast carcinogenesis [19], and the other one is XMRV (xenotropic murine leukemia-related virus), a chimeric, laboratory-derived gammaretrovirus that, interestingly, arose from the recombination of two endogenous mouse viruses. XMRV was suspected to be associated with prostate cancer [20].

Bacterial infections

The prototype of cancer-associated bacteria is *H. pylori*, which is categorized in IARC Group 1 and was responsible for the 5.5% of cancers in the world in 2002 [7] and for the 5.2% in 2008 [8]. It has been estimated to account for the 63.4% [7] or 80.0% [19] of gastric cancers, specifically non-cardia gastric cancer. In addition, the chronic infection of the stomach with this bacterium is associated with MALT (mucosa-associated lymphoid tissue lymphoma). The intriguing issue is that about two-thirds of the world population, with some geographic variations, are carriers of *H. pylori*, and luckily only a small fraction of colonized individuals develop gastric cancer. We demonstrated that both bacterial and host gene polymorphisms affect oxidative stress and DNA damage, which is believed to represent a key mechanism in the pathogenesis of gastric cancer [21].
Among other bacteria, *Salmonella typhi* and *Streptococcus bovis* have been suspected of being associated with gallbladder carcinoma and colorectal cancer, respectively [22]. The persistent infection of erythrocytes and endothelial cells with Bartonella can trigger angiogenesis and lead to vascular tumor formation in humans, and *Chlamydophila pneumoniae* has been suspected of being associated with lung cancer [23].

Protozoan infections

Plasmodium falciparum infection in holoendemic areas is probably carcinogenic to humans (IARC Group 2A) because, in the absence of any adequate evidence in experimental animals, there is limited evidence for an association between malaria caused by infection with that protozoan species and cancer. In particular, it is well demonstrated that *P. falciparum* reactivates EBV thereby contributing to Burkitt's lymphoma etiology [11].

Trematode infestations

Some of the flatworms belonging to the Schistosoma genus, also known as blood flukes, have been investigated for their association with human cancers, especially in certain geographical areas. There is sufficient evidence for the ability of *S. haematobium* to cause urinary bladder cancer, whereas *S. japonicum* is possibly associated with colorectal and liver cancers, and there is inadequate evidence for the carcinogenicity of *S. mansoni.* Among the flatworms known as river flukes, there is sufficient evidence for the role of *Opistorchis viverrini* in inducing cholangiocarcinoma, while the evidence for *Opistorchis felineus* is evaluated to be inadequate. The same cancer is associated with infestation of the human common bile duct and gallbladder with the Chinese liver fluke (*Clonorchis sinensis*) [9].

Prevention strategies for infection-associated cancers

Primary prevention

The primary prevention of infection-related cancers is addressed both to avoid and eradicate chronic infections and infestations and to defend the host organism at a time when a subject is still apparently healthy. Therefore, the first line of defence is to prevent the infectious and parasitic disease, a goal that can be pursued by means of both aspecific and specific measures.
Vaccines play a fundamental role among the specific tools available to prevent some cancer-related infections. While the development of candidate vaccines against certain agents, such as HCV, HIV, *H. pylori*, and *P. falciparum*, is still in progress and suffers from technical problems, other vaccines are extensively used worldwide and hold great promises in cancer prevention. One of them is the hepatitis B vaccine, which has been introduced into routine infant immunization programs since 1992. The impact of anti-HBV vaccination on HCC epidemiology has already been demonstrated in Taiwan, where the universal HBV vaccination program, launched in 1984, reduced the prevalence of HBV to approximately one-tenth. In parallel, evidence was provided that HCC incidence was decreased as a consequence of the vaccination in children aged 6-14 years and, later on, also in early adulthood [24]. Failures to prevent HCC depended mostly on the unsuccessful control of HBV infection of maternal origin. Besides early vaccination of infants, administration of hepatitis B immunoglobulin immediately after birth, and even antiviral agent during the third trimester of pregnancy are possible strategies to block mother-to-infant transmission of HBV and to prevent HCC [25].
The HBV vaccine is the first example of cancer-preventive vaccine in humans, proving evidence that prevention of an infectious disease can prevent the related cancer. On the other hand, HPV vaccines are the first example of vaccines that have specifically been designed to prevent HPV-related cancers in humans. In fact, these vaccines, containing the HPV envelope protein L1 obtained by recombinant DNA techniques [23], target the HPV types responsible for the majority of cervical cancers and of non-cervical cancers as well. It can been foreseen that, together with secondary prevention, HPV vaccines will be successful in further reducing the burden of CIN (cervical intraepithelial neoplasia) and of HPV-related cancers.
Since infections need to become persistent in order to trigger the development of cancers, whichever is their mechanism of action, a further primary prevention strategy is to avoid chronicization of the disease. Thus, it is intriguing that the therapy of an infectious and parasitic disease becomes a tool to prevent the associated cancer. Besides a broad variety of drugs available to cure specific infectious diseases, examples of this kind of prevention include the HAART (high active antiretroviral therapy) for HIV infections, the new drugs avail-

able for the treatment of chronic hepatitis B and C, and the treatments to eradicate *H. pylori* infection in healthy asymptomatic subjects. For instance, in the Shandong Intervention Trial, two weeks of antibiotic treatment for *H. pylori* reduced the incidence of both precancerous gastric lesions and gastric cancer [26].

Furthermore, it should be taken into account that cancers are multifactorial in origin and that, besides infectious agents, other factors may contribute to the risk of developing the same cancers. Such a circumstance involves the implementation of integrated strategies for the primary prevention of these cancers. An extreme example is provided by HPV infections. Although HPV infections cause almost the 100% of cervical cancer cases, HPV can interact with other co-factors, such as tobacco smoking, hormonal contraceptive use, intake of nutrients, and co-infections with HSV (Herpes Simplex Virus) or *Chlamydia trachomatis* [27]. Other examples of interactions are either between different infectious agents, e.g., between HIV and KSHV in the pathogenesis of Kaposi's sarcoma or between EBV and *P. falciparum* in the pathogenesis of Burkitt's lymphoma, or between infectious agents and chemical carcinogens. For instance, the synergism between HBV and chemical hepatocarcinogens requires integrated strategies addressed to prevent chronic hepatitis B, to avoid exposures to chemical carcinogens, and to reinforce the body defence mechanisms by means of dietary and pharmacological agents.

SECONDARY PREVENTION

In case primary prevention fails avoiding the occurrence of a neoplastic lesion and the carcinogenic process starts its course, it is still possible to apply secondary prevention. Its goal is to detect a preneoplastic or a neoplastic lesion at an early stage and to intervene timely in order to stop progression of cancer.

An infection-associated cancer, the HPV-related cervical cancer, provides the most classical example of secondary prevention. The cytological analysis of epithelial cell smears, introduced by George Papanicolau more than 80 years ago, meets all the criteria requested for an oncological screening, from the epidemiological relevance of the disease to the poor invasivity of cell collection, fair performance of the test, low cost, and availability of a therapy to cure the disease. The large-scale application of the Pap test has remarkably reduced the burden of cervical cancer in all developed countries and has driven a wedge between different geographical areas. More recently, the HPV DNA testing, which analyzes the DNA of high risk HPV (HR HPV) in cervical cells, has been introduced and proposed to replace the Pap test as a first-screen method. This molecular approach detects an ongoing infection with HR HPV, which just testifies the risk of developing cervical cancer rather than an HPV-related cytological alteration. Thus, it is more sensitive but less specific and it needs confirmation by means of a cytological test and, if necessary, of colposcopy and biopsy.

Another example of secondary prevention applied to an infection-associated cancer is early gastric cancer, in which the disease is limited to mucosa and submucosa, so that removal of the lesion confers a survival rate after 5 years of 90%. Regression of premalignant lesions has been demonstrated after *H. pylori* eradication. Asian countries have implemented national screening programs for the detection of early gastric cancer, but in Western countries mass screening is not cost-effective and strategy has been directed to screen symptomatic individuals who are at higher risk of gastric cancer [28]. Serology testing for biomarkers such as pepsinogen, anti-*H. pylori* antibody and gastrin have been studied as an alternative to endoscopy [28].

TERTIARY PREVENTION

In the framework of the oncological patient management, tertiary prevention is addressed to cancer patients after therapy and it has the goal toprevent local relapses, invasion, and metastasis [29]. It can be pursued either by treating the cancer-related infection, e.g., by using antiviral agents to prevent recurrences in HBV-positive patients who have been cured for HCC [25], and/or by treating the neoplastic lesion. Besides traditional cytostatic drugs, the pharmacological armamentarium available for cancer therapy and tertiary prevention has been strengthened by introducing a variety of "smart drugs" that, rather than aspecifically kill cancer cells, try to target specific molecular mechanisms involved in cancer development and growth. A promising approach is to inhibit angiogenesis, which is a crucial mechanism in several infection-related cancers, by targeting VEGF (vascular endothelial growth factor) and other pro-angiogenetic factors [30]. Examples are HCC, having a hypervascular nature [31], bartonella-induced vascular tumors, and HIV/ KSHV-related Kaposi's sarcoma, which is a highly vascularized cancer. We demonstrated that the oral administration of the antioxidant agent NAC (*N*-acetylcysteine) reduced tumor growth in nude mice xenotransplanted with human KS cells and, in some cases, there was a complete regression of the neoplastic mass [32].

Conclusions

The prevention of infection-associated cancers would be expected to control an important fraction of human cancers. Compared with cancers having a non-infectious nature, in principle these cancers would appear to be more easily avoidable because, besides the other strategies applicable to cancer prevention, it is sufficient to protect the body from exogenous pathogenic agents and to hamper the persistence of infections. Indeed, both primary prevention and secondary prevention measures have already proven to be successful in fighting certain cancers associated with infectious and parasitic diseases, which is highlighted by the sharp disparities between developed and developing countries in the incidence of these cancers. Future objectives in the prevention of infection-associated cancers include the improvement of our scientific knowledge about the mechanisms in-

volved, the development of new tools for the control of both infectious diseases and associated cancers, and the application of preventive measures on a global scale in order to fill the gap existing among different regions in the world.

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