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REVIEW

The prevention of infection-associated cancers

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Collectively, chronic viral and bacterial infections and trematode infestations have been estimated to be associated with approximately one of five human cancers worldwide. The fraction attributable to each one of the chronic infections caused by hepatitis B and C viruses (HBV and HCV), human papillomaviruses (HPV) and *Helicobacter pylori*, is ∼5%. These infections are the most important causes of major types of cancer, including hepatocellular carcinoma, cervical cancer and stomach cancer, respectively. Taking into account the mechanisms of infection-related carcinogenesis, integrated approaches are addressed to the control of the associated infection as well as to avoidance of cancer occurrence and progression. Large-scale interventions have been implemented, such as the anti-HBV and anti-HPV routine vaccination programs. The latter has been designed with the specific goal of preventing HPV-associated cancers, which is an outstanding breakthrough in cancer prevention. Intriguingly, not only prevention but even therapy of an infectious disease and eradication of a pathogen become a crucial tool for the primary prevention of these cancers. An important role is also played by secondary prevention (e.g. Pap test and DNA testing for HPV-associated cervical cancers) and by tertiary prevention (e.g. antiangiogenesis in Kaposi's sarcoma). The present article reviews the microbial and parasitic diseases that have been associated so far with human cancers, draws an overview of their burden in cancer epidemiology, deals with applicable prevention strategies and provides examples of co-ordinated approaches to the control of cancers associated with HBV, HCV, HPV, human immunodeficiency virus and *H.pylori* infections.

Overview of microbial and parasitic diseases associated with human cancers

While the discovery that viruses can cause tumors in animals traces back to 1 century ago (1), the implication of microbial and parasitic diseases in the causation of human cancers has been demonstrated more recently. The burden of infection-associated cancers depends on a variety of factors. An important one is the geographic area, since certain chronic viral and bacterial infections and trematode infestations have a greater epidemiological impact in developing countries, as compared with developed countries, where only 16% of the world population resides. This circumstance is due to the higher endemicity, in developing countries, of infectious and parasitic diseases posing carcinogenic risks and to the lower availability of both preventive and therapeutic tools aimed at curing the disease or at avoiding its chronic evolution.

Abbreviations: AFB_1, aflatoxin B_1; AIDS, acquired immune deficiency syndrome; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HHV, human herpesvirus; HIV, human immunodeficiency virus; HPV, human papillomavirus; HTLV, human T-cell lymphothropic (T-cell leukaemia/lymphoma) virus; IARC, International Agency for Research on Cancer; ILinterleukin, ; KSHV, Kaposi's sarcoma herpesvirus; MALT, gastric B-cell mucosa-associated lymphoid tissue lymphoma; SV40, simian virus 40.

The proportions of cancer deaths attributable to viral and bacterial infections and to parasitic diseases were tentatively estimated by Doll *et al.* (2) to be 10% in the USA in 1981 and by Doll to be 10–20% in UK in 1998 (3). Pisani *et al.* (4) estimated that 15.6% (1 450 000 cases) of the worldwide incidence of cancers in 1990 could be attributed either to hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomavirus (HPV), Epstein–Barr virus, human T-cell lymphothropic (T-cell leukaemia/lymphoma) virus (HTLV)-1, human immunodeficiency virus (HIV), *Helicobacter pylori*, schistosomes or liver flukes. These data were updated in 2006 by Parkin (5) who, based on the evidence of the strength of association and the prevalence of infection in different geographic areas, estimated that the total infection-attributable cancer in the year 2002 was 1.9 million cases, which accounted for 17.8% of all cancers in the world. By preventing cancer-associated infectious diseases, there would be 26.3% fewer cases in developing countries (<1.5 million cases/year) and 7.7% fewer cases in developed countries (<390 000 cases) (5). In 2009, zur Hausen (6) estimated that slightly >20% of the global cancer burden can be linked to infectious agents and predicted that this fraction will increase in the future.

Table I provides an outline of the infections and infestations that have been associated so far with specific cancers in humans. A number of them have been categorized, according to the criteria of the International Agency for Research on Cancer (IARC), either in Group 1 (carcinogenic to humans), Group 2A (probably carcinogenic to humans), Group 2B (possibly carcinogenic to humans) or Group 3 (not classifiable as to carcinogenicity to humans). Of the microbial types and parasitic species evaluated so far by IARC (Volumes 1–100), 22 are categorized in Group 1, 1 in Group 2A and 16 in Group 2B. The last column in Table I reports the estimates made by Parkin (5) regarding the fraction of cancer attributable to specific infectious agents. It can be noted that the three major cancer-related infections are cumulatively associated with 15.6% of all human cancer cases in the world.

The infections with HBV and HCV, which are the only hepatitis virus infections that tend to evolve chronically, are associated with occurrence of hepatocellular carcinoma (HCC). These two viruses are quite different from both taxonomic and structural standpoints. In fact, HBV is a DNA virus that belongs to the family of hepadnaviridae, together with other hepatotropic viruses that are pathogenic to animal species other than humans, among which the woodchuck hepatitis virus shares strict analogies with HBV also with respect to HCC pathogenesis. HCV is a positive-strand RNA virus related to the family of flaviviridae. Hepatitis D virus, also known as hepatitis delta antigen (HDAg), has a circular RNA genome and needs concurrent infection with a hepadnavirus for its replication. Although it has been shown that chronic hepatitis and cirrhosis develop more rapidly in case of HBV superinfection with Hepatitis D virus, there is no adequate demonstration of Hepatitis D virus contribution to HCC (7). HBV and HCV infections were estimated to be associated with 4.9% of all cancer cases and specifically with 85.5% of all HCC cases in the world, 54.4% of which attributable to HBV and 31.1% attributable to HCV according to Parkin (5). A similar figure (80.0%) was confirmed by zur Hausen (6). Liver cancer is the third leading cause of cancer death in men and the sixth among women, with an expected number of 680 000 deaths in 2007 (23).

Papillomaviruses and polyomaviruses are DNA viruses that formerly belonged to the family of papovaviridae, together with simian virus 40 (SV40) or vacuolizing virus. In fact, the papova prefix combines the two initial letters of papilloma, polioma and vacuolizing. The present taxonomy classifies papillomaviruses in the family of papillomaviridae, whereas both polyomaviruses and

Table I. Viral and bacterial infections and trematode infestations associated with cancer in humans

Pathogen	IARC group	Main associated cancer	Attributable cancer % (5)
Hepatitis viruses			4.9
HBV	1	HCC (7)	
HCV	1	HCC (7)	
HDV	3	None (7)	
Papillomaviruses (HPV)			5.2
Alpha HPV type 16	1	Cancers at several sites (8)	
Alpha HPV types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59	1	Cervical cancer (9)	
Alpha HPV type 68	2A	Cervical cancer (9)	
Alpha HPV types 26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85, and 97	2B	Cervical cancer (9)	
Beta HPV types 5 and 8	2B	Skin cancer (9)	
Alpha HPV types 6 and 11	3	None (9)	
Other beta and gamma HPV types	3	None (9)	
Polyomaviruses			
JCV	NA	CNS tumors (10) and colorectal cancer? (11)	
MCV	NA	Skin cancer (Merkel cell carcinoma) (12)	
SV40	NA	Malignant mesothelioma? (13,14)	
Herpesviruses			
EBV or HHV4	1	Burkitt's lymphoma, sinonasal angiocentric T-cell lymphoma, immunosuppressor-related non-Hodgkin's lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma (15)	1.0
KSHV or HHV8	1	Kaposi's sarcoma (15), primary effusion lymphoma (8)	0.9[a]
Retroviruses			
HTLV-I	1	Adult T-cell leukemia/lymphoma (8,16)	0.03
HTLV-II	3	None (16)	
HIV-1	1	Kaposi's sarcoma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, cervical cancer, anus cancer, conjunctive cancer (8,16)	
HIV-2	2B	Kaposi's sarcoma, non-Hodgkin's lymphoma (8,16)	
HERV-K	NA	Human breast cancer (6)	
XMRV	NA	Prostate cancer (17)	
Helicobacter pylori	1	Non-cardia gastric cancer, MALT lymphoma (8,18,19)	5.5
Streptococcus bovis	NA	Colorectal cancer (18)	
Salmonella typhi	NA	Gallbladder cancer (18)	
Bartonella species	NA	Vascular tumours (20)	
Human gut microbiome	NA	Colon cancer (21)	
Clamydophila pneumoniae	NA	Lung cancer (18,22)	
Schistosomes			0.1
Schistosoma haematobium	1	Urinary bladder cancer (19)	
Schistosoma japonicum	2B	Colorectal and liver cancers (19)	
Schistosoma mansoni	3	None (19)	
Liver flukes			0.02
Opistorchis viverrini	1	Cholangiocarcinoma (19)	
Opistorchis felineus	3	None (19)	
Chlonorchis sinensis	1	Cholangiocarcinoma (8,19)	

Abbreviations: HDV, hepatitis D virus (Delta agent); HERV-K, human endogenous retrovirus-K; JCV, JC virus; CNS, central nervous system; MCV, Merkel cell virus; EBV, Epstein–Barr virus; XMRV, xenotropic murine leukemia virus-related virus.
[a]Together with HIV infection.

SV40 are in the family of polyomaviridae. HPV include >100 types, whose infection may become persistent and then progress to precancerous lesions and eventually to invasion by causing cancers in a variety of sites, including uterine cervix, vulva, vagina, penis, anus, oral cavity, oropharynx and possibly the skin in patients with epidermodysplasia verruciformis (8). Recently, as summarized in Table I, the IARC Working Group has reclassified the carcinogenicity of alpha, beta and gamma HPV types in Groups 1, 2A, 2B and 3 (9). HPV infections were estimated to account for 5.2% of all cancers in the world, being responsible for 3% of mouth cancers, 12% of oropharynx cancers, 40% of penis cancers, 40% of vulva/vagina cancers and virtually 100% of uterine cervix cancers (5). Cervical cancer is the second most commonly diagnosed cancer in women and is the third leading cause of cancer death in women worldwide. An estimated 309 800 deaths were expected to occur in 2007, >83% of which in developing countries (23).

Among polyomaviruses, JC virus causes a fatal-demyelinating disease, the progressive multifocal leukoencephalopathy. JC virus is tumorigenic to several animal models and is suspected to be carcinogenic also to humans due to an increased incidence of central nervous system tumors (10) and colorectal cancer (11) in progressive multifocal leukoencephalopathy patients. The Merkel cell virus is the etiological agent of a skin cancer known as Merkel cell carcinoma (12). SV40 is an extensively investigated oncogenic virus to rodents, which was a contaminant of live poliovirus vaccines that were administered to millions of children between 1955 and 1963. It has been suspected that SV40 may be associated with human malignant mesothelioma, due to the detection of viral DNA sequences in this cancer. However, this issue is controversial (13,14).

Two DNA viruses belonging to the subfamily of gammaherpesviridae have been shown to be involved in the causation of human cancers. The Epstein–Barr virus or human herpesvirus (HHV) 4, belonging to the Lymphocryptovirus genus, is the etiological agent of infectious mononucleosis during adolescence and young adulthood. HHV4 is associated with multiple cancers and specifically with several types of lymphoma and with nasopharyngeal carcinoma

(15). The other herpesvirus, discovered in patients affected by acquired immune deficiency syndrome (AIDS), is denominated Kaposi's sarcoma-associated herpesvirus (KSHV) or HHV8, which is also related to primary effusion lymphoma (9).

Besides HCV, other RNA viruses that have been associated with human cancers belong to the family of retroviridae. The virion of the HTLV contains two genomic RNA strands complexed with various enzymes, among which reverse transcriptase. HTLV-I has been associated with T-cell leukemia/lymphoma, whereas the evidence for HTLV-II carcinogenicity is so far inadequate (16). The HIV-1, initially denominated HTLV-III or lymphoadenopathy-associated virus, and the structurally related HIV-2, classified in the group of lentiviruses, are the etiological agents of AIDS. Their virion has a single-stranded RNA genome within a protein core that contains reverse transcriptase. The severe immunodeficiency caused by HIV-1 has been associated with several human cancers and especially with Kaposi's sarcoma and non-Hodgkin's lymphoma, and a similar association is possibly involved also with HIV-2 (16). Recently identified human endogenous retroviruses (HERV), and in particular human endogenous retrovirus-Q, play a potential role in the pathogenesis of human breast cancer (6). The xenotropic murine leukemia virus-related virus, the first gammaretrovirus known to infect humans, has been associated with prostate cancer, especially high-grade tumors (17).

Several bacteria are known or suspected to be related to cancers in humans (18). The most important is *H.pylori*, formerly named *Campylobacter pyloridis* or *C.pylori*, a spiral or slightly curved gram-negative bacterium with two to six characteristic unipolar flagella, which is the main cause of chronic gastritis in humans and has been associated with both gastric cancer and gastric B-cell mucosa-associated lymphoid tissue lymphoma (MALT) (8,18,19). *Helicobacter pylori* was estimated to be associated with 5.5% of all cancers and specifically with 63.4 (5) or 80.0% (6) of stomach cancers. Note that stomach cancer, in 2007, was expected to remain the fourth most common malignancy in the world, with 1 million new cases, 70% of which in developing countries (23).

Of other possible bacteria related to cancer, *Streptococcus bovis* is a normal inhabitant of the human gastrointestinal tract that, according to several studies, may be involved in colorectal carcinogenesis (18). Chronic infection of the gallbladder with *Salmonella typhi* increases the risk of developing gallbladder carcinoma (18). Arthropod-borne bartonellae cause persistent infection of erythrocytes and endothelial cells, whose massive proliferation can lead to vascular tumor formation in humans (20). Besides exogenous bacteria, it has been suspected that indigenous microbes may play a role in cancer risk because they are part of our metabolism and makeup (21). The human gut microbiome has been implicated in the etiology of localized intestinal diseases such as the irritable bowel syndrome, inflammatory bowel disease and colon cancer (24). In addition, there is epidemiological evidence that the obligate intracellular *Chlamydophila* (formerly *Chlamydia*) *pneumoniae* may be associated with chronic lung diseases, also including lung cancer (18,22).

In addition, infestations with trematode worms belonging to the phylum Platyhelminthes have been associated with human cancers. The association of *Schistosoma haematobium* infestation with urinary bladder cancer is well established, whereas infestation with *Schistosoma japonicum* is possibly associated with colorectal cancer and liver cancer (19). Both *Opistorchis viverrini* and *Chlonorchis sinensis* infestations are convincingly demonstrated to be associated with occurrence of cholangiocarcinoma (8,19).

Thus, on the whole, it appears that persistent infections are the leading causes for some of the most important human cancers, such as stomach cancer, cervical cancer and liver cancer. Collectively, their impact on human cancer epidemiology is just lower than that of the two dominating, lifestyle-related causes of cancer, i.e. tobacco smoking and dietary factors. Individually, the risk attributable to each one of the three major viral (HPV, HBV/HCV) and bacterial (*H.pylori*) chronic infections is higher than that attributable to important risk factors, such as environmental pollution.

It has been suggested that the burden of infection-related cancers is still underestimated worldwide due to the use of conservative population prevalence and risk ratio estimates (25). In estimating the global burden of cancer, Thun *et al.* (26) have predicted that, in the next 40 years, the demographic shift towards an increased longevity is compounded by the entrenchment of modifiable risk factors such as smoking and obesity in many low- and medium-resource countries and by the slower decline in cancers related to chronic infections in economically developing countries.

Prevention strategies for infection-associated cancers

In principle, the control of infectious diseases and of cancer requires differentiated prevention strategies. Thanks to the discovery of bacteria, viruses and other pathogens since the late 1800, the man–environment binomial, also known as Hippocrate's dyad, has become a triad by incorporating the etiological agents. In such a way, it has been possible to achieve extraordinary results in the control of morbidity and even more of mortality of infectious diseases (27). Clearly, there are important exceptions, especially in certain geographical areas. Since the etiological agent is the necessary but not sufficient cause of an infectious disease, its removal implies the absence of that disease. In contrast, cancer has a multifactorial origin and depends on the interplay of multiple factors, either physical or chemical or biological. As a consequence, removal of a single risk factor will never succeed in eradicating a given cancer because the same cancer is at the same time linked to other risk factors. There may be exceptions to this assumption in cases where the totality of a given cancer is attributable to a single cause, as exemplified by uterine cervix cancer caused by HPV infection (19).

Preventive medicine can be applied at three levels. Primary prevention is addressed to apparently healthy individuals with the goal of preventing occurrence of the disease. Secondary prevention is addressed to patients in preclinical or early stage with the goal of detecting early lesions and preventing progression of the disease. Tertiary prevention is addressed to cancer patients after therapy with the goal of preventing local relapses, invasion and metastasis (28,29).

Integrated strategies should be applied in the prevention of infection-related cancers because they need to be addressed to the control of the associated infections as well as to avoidance of cancer occurrence and progression. Figure 1 gives the rationale for the prevention of infection-associated cancers as related to the growth of the neoplastic mass and to the steps of the carcinogenesis process. Starting from a single cell, doubling of the population of tumor cells will generate 10^9 cells after 30 divisions. At this stage, the weight of the neoplastic mass may be $\sim$1 g, and for some cancers, this may be the appropriate time for applying secondary prevention. A paradigmatic example is provided by an infection-associated cancer, i.e. uterine cervix cancer. The Pap test, introduced by George Papanicolau (30) in 1928 and reported in a paper published in 1941, represents the oldest example of early cancer diagnosis and the most extensively used screening test applied to the secondary prevention of cancer (31). In addition, in more recent years, the HPV DNA testing was introduced in cervical cancer screening strategies. HPV DNA can be identified in nearly all specimens of invasive cervical cancer and in the vast majority of high-grade squamous intraepithelial lesions, also known as cervical intraepithelial neoplasia 3 or carcinoma *in situ* (32,33). Another example of secondary prevention of a predominantly infection-associated cancer is provided by stomach cancer. Japan and certain other Asian countries have implemented national screening programs for the endoscopic detection of early gastric cancer (34–36). Molecular techniques for identifying pathogens associated with cancer continue to be developed (37). A genome-wide approach, called Digital Karyotyping Microbe Identification (DK-MICROBE), has been developed to identify genomic DNA of bacteria and viruses, also including previously unknown infectious agents in human tumors (38).

In case no intervention is made and no spontaneous regression occurs, an event that is always possible at a premalignant stage, the

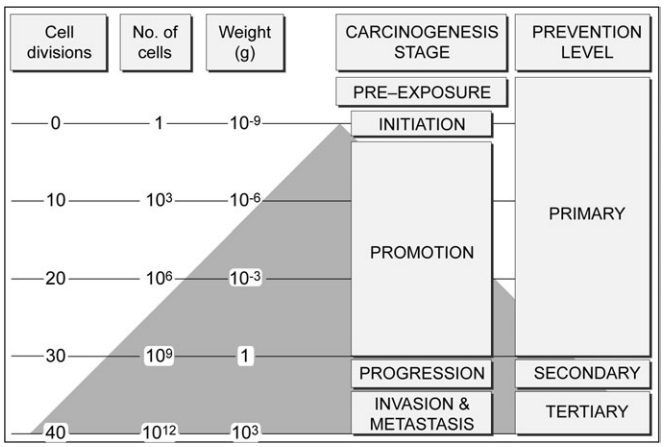

Fig. 1. Cancer prevention levels as related to the growth of the neoplastic mass and to the steps of the carcinogenesis process. The triangular dashed area depicts, on a logarithmic scale, the growth of the neoplastic mass.

carcinogenesis process will progress and, in 10 divisions only, from the 30th to the 40th division, the neoplastic mass will grow from 1 g to 1 kg. Among the various protective mechanisms that can be exploited in advanced carcinogenesis stages, inhibition of angiogenesis is particularly promising (29). Again, a relevant example is provided by infection-associated cancers. In fact, Kaposi's sarcoma, which is associated with both KSHV/HHV8 infection and HIV-related immunodeficiency, is a highly vascularized tumor with a dense, poorly organized network, a feature that is expected to render it particularly susceptible to antiangiogenic agents (39). The angiogenic nature of Kaposi's sarcoma, which results from reactive hyperproliferation induced by chronic inflammation, makes this condition particularly suitable to the application of therapies based on targeted agents, such as metalloproteinase inhibitors, tyrosine kinase inhibitors and angiogenesis inhibitors (39). Studies in nude mice transplanted with Kaposi's sarcoma cells showed that the oral administration of the chemopreventive agent *N*-acetylcysteine produces a sharp reduction of tumor growth, leading to a complete regression of tumors in half of the treated mice (40). Another example is HCC, having a hypervascular nature. Antiangiogenic treatment can be effective for both HCC chemoprevention and tumor dormancy (41).

As to primary prevention, as shown in Figure 1, it is possible to lower the risk of infection-associated cancers either during the pre-exposure period or during the initiation and promotion stages, until the cancer becomes clinically manifest. This kind of intervention is first of all addressed to prevention of the specific infectious disease that lies at the root of cancer. The use of vaccines against cancer-associated pathogens is one of the most promising areas of ongoing cancer prevention research. Prophylactic vaccines against pathogenic viruses have an excellent record as public health interventions in terms of safety, effectiveness and ability to reach economically disadvantaged populations (42,43). When an infection or infestation is established, a further step is to eliminate the pathogen from the organism and to avoid evolution towards persistency. Indeed, it is intriguing that not only prevention but even therapy of an infectious disease may become a crucial strategy for the primary prevention of approximately one of five human cancers.

A complementary primary prevention approach is to contrast the mechanisms leading to initiation and promotion of tumors in infected but apparently cancer-free individuals. Although less obvious, this kind of intervention is quite important also because the latency period elapsing between the start of infection and cancer development is frequently in the range of 15–40 years (11). Therefore, understanding the mechanisms responsible for neoplastic transformation in infected individuals is essential for the development of protective pharmacological agents or implementation of dietary chemoprevention regimens. A great variety of mechanisms, both genetic and epigenetic, have been hypothesized or demonstrated to be involved. They include, for instance, the introduction of viral oncogenes into host cells, mutations in host cell genes, induction of chromosomal instability and translocations, altered gene expression, oxidative stress, chronic inflammation, stimulation of cell proliferation, inhibition of apoptosis, immunosuppression and interaction with chemical carcinogens (11,44–46). The major mechanisms by which infectious agents can promote and maintain tumor formation have been divided broadly into three main categories, including chronic inflammation, virus-induced transformation and chronic suppression of the immune system (37). Among other mechanisms that can be exploited for the prevention of virus-related cancers, interferons are of particular interest, because these cytokines induce a number of tumor suppressor genes and may play an important role in the control of cell proliferation (47).

Primary prevention of major infection-associated cancers

In addition to implementation of specific intervention measures, the primary prevention of cancer-associated infections has to take into account general prevention strategies related to the transmission routes of those viruses, bacteria and trematodes that pose a carcinogenic risk. A limited number of them, such as schistosome infestations, are transmitted via skin contact with the substrate where the parasite is present (e.g. lake water). *C.pneumoniae* and HHV4 infections are airborne. HHV4 is characteristically transmitted with saliva. Liver fluke infestations and some bacterial infections, such as *S.bovis* and *S.typhi* infections, follow the fecal–oral route and are thus, dirty hand diseases that are mainly transmitted through contaminated food and water. Water has been also implicated as a potential source of infection with *H.pylori*, but direct person-to-person contact is its most probable mode of transmission (48). Interestingly, the majority of the viral infections that tend to chronicize and to be associated with cancer, such as HBV, HCV, HPV, HHV8, HTLV-I, HTLV-II, HIV-1 and HIV-2 infections, involve parenteral and sexual transmission routes. Thus, sexual transmission is a major route for virus-related cancers.

Another critical issue in the genesis of infection-associated cancers is the possible occurrence of interactions between different microorganisms or between microorganisms, hormones or chemical carcinogens, which requires integrated strategies for their primary prevention. For instance, immunodepression by HIV may favor KSHV/HHV8 infection and occurrence of Kaposi's sarcoma (16). There is a well-established relationship between endemic *Plasmodium falciparum* malaria and Epstein–Barr virus/HHV4 infection in the pathogenesis of Burkitt's lymphoma, which is regarded as a polymicrobial disease (49). Female sex hormones are known to regulate susceptibility and immune response to sexually transmitted viral infections, such as HIV and HPV infections (50). A strong correlations exists between smoking and oncogenic HPV (51). Likewise, tobacco use increases susceptibility to *H.pylori* and other bacterial infections, presumably by compromising the antibacterial function of leukocytes including neutrophils, monocytes, T cells and B cells (52). A further important example of interaction between viruses and chemical carcinogens, which will be discussed below, is the synergism between chronic HBV/HCV infections and either aflatoxin B_1 (AFB_1) intake with food or alcohol drinking in the pathogenesis of HCC (53,54).

Examples of primary prevention approaches for cancers associated with four viral infections (HBV, HCV, HPV and HIV) and one bacterial infection (*H.pylori*), having an attributable cancer risk >1% each (see Table I) will be discussed below. Next sections do not pretend to thoroughly cover the whole literature dealing with the prevention of these infections but are intended to provide information relevant to the prevention of the associated cancers.

HBV-associated HCC

HBV is one of the most contagious infectious agents. Its ability to be transmitted not only via direct contact with virus carriers but also to

survive for several months in the external environment under appropriate conditions (e.g. inclusion in organic materials such as dried blood) as well as the possibility to infect susceptible subjects with a very small viral inoculum, explain its high incidence in the world population. After 20–30 years of chronic infection, 20–30% of HBV carriers will develop liver fibrosis and then cirrhosis, which is a precursor condition to 80–90% of all HCCs (55). In addition to cirrhosis and the resulting chronic inflammation and hyperproliferation, several mechanisms have been proposed for explaining this association. Integration of HBV-DNA in the host genome results in the intracellular synthesis of HBV proteins, such as pre-S2/S and HBx protein (HBxAg), that transactivates several cytoplasmic signaling pathways. A wide range of genetic alterations occur in the host genome, including chromosomal deletions, translocations, production of fusion transcripts, amplification of cellular DNA and genomic instability. These events often occur near fragile sites and alter the expression of oncogenes, tumor suppressor genes and microRNAs (55). An additional important mechanism in HCC causation is the interplay between chronic hepadnavirus infection and chemical hepatocarcinogens. Epidemiological studies have shown that, in South-East Asia and sub-Saharian Africa, there is a multiplicative interaction between HBV infection and the mycotoxin AFB_1 in terms of HCC risk (53). A synergism has been also demonstrated between alcohol drinking and infection with either HBV or HCV (54). There is an enhanced metabolic activation of chemical hepatocarcinogens, and especially of heterocyclic amines, both in HBV-infected hepatocytes (56) and in woodchuck hepatitis virus-infected hepatocytes (57–59). These food-derived mutagens induce cancer in the liver and other organs when given to rodents in the diet (60).

In this light, it appears that the primary prevention of HBV-related HCC requires integrated strategies, as summarized in Figure 2. The fulcrum is the prevention of HBV infection and of its chronicization. Both controlled studies and meta-analyses have demonstrated that therapy with interferon and lamivudine of chronic hepatitis B patients significantly reduces progression to cirrhosis and HCC (61,62), and that interferon-related decrease of serum HBV-DNA prevents HCC development (63). In addition, primary prevention is addressed to chemical carcinogens that, either *per se* or in combination with hepatotropic viruses, can cause HCC. The obvious approach is to avoid exposures to these agents either through suitable regulations, such as the control of food for the presence of AFB_1, or through health education informing the population about the risks resulting from an excessive broiling of food or alcohol intake. Complementarily, chemoprevention of HCC can be pursued by means of pharmacological and dietary agents, especially in high-risk areas. Modulation of AFB_1 disposition can be achieved through induction of conjugating and cytoprotective enzymes, which are regulated via Kelch ECH-associating protein 1 (Keap1)-NF-E_2-related factor 2 (Nrf2)-antioxidant response element signaling (64). For example, phase II clinical intervention trials were conducted in Qidong, Jiangsu Province, People's Republic of China, using either dietary or pharmacological agents, such as phenolic antioxidants, dithiolethiones, isothiocyanates and triterpenoids (64–68).

One of the most important measures of prevention for HBV infection was the introduction, since 1975, of HBV surface antigen screening of all blood donations. Posttransfusion acute hepatitis, which usually occurred in as much as 25% of recipients in the prescreening era, dramatically dropped to $\sim$10% in few years, further decreasing to $<$1% after the discovery, in 1989, of the main agent responsible for non-A, non-B hepatitis, named HCV (69,70). Other general preventive measures consist in the application of universal precautions for infections transmitted through blood and other body fluids (71,72).

Since the introduction of the first plasma-derived hepatitis B vaccines at the beginning of the eighties, followed by the availability of second generation vaccines obtained by recombinant-DNA techniques, immunization recommendations have evolved from use focused on risk groups to universal vaccination of all newborns or infants (73). Infant immunization was coupled with adolescent vaccination in several countries. The World Health Assembly recommended introducing hepatitis B vaccine into routine infant immunization programs in all countries since 1992. As of July 2009, 177 countries in the world had complied with such recommendation. The experience with universal hepatitis B vaccination programs in Taiwan, one of the highest endemicity countries for HBV, where a universal vaccination program was launched in 1984, already demonstrated the dramatic importance of vaccination for cancer prevention. The average annual incidence of HCC in children aged 6–14 years declined from 0.70 per 100 000 between 1981 and 1986 to 0.57 between 1986 and 1990, and to 0.36 between 1990 and 1994. The corresponding rates of mortality from HCC also decreased since the fatality rates for HCC are close to 100% (74). Therefore, the incidence of HCC in children had already significantly declined 10 years after implementation of the universal vaccination program (75). A more recent evaluation, after 20 years of follow-up, showed that HCC incidence was significantly lower among children aged 6–19 years in subjects belonging to vaccinated cohorts compared with unvaccinated birth cohorts (76).

So far, the Taiwanese data are the only available on the effectiveness of anti-HBV vaccination against HCC. However, large vaccination trials in Qidong, China and in The Gambia are presently under way, and within the next few years, they will be able to provide comparative estimates of incidence of HCC in young adults born before or after the introduction of the vaccine. The public health impact of universal hepatitis B infant/newborn vaccination on the decline of chronic liver disease and HCC is expected to be impressive (77).

HCV-associated HCC

More than 170 million people are chronically infected with HCV worldwide, and there are 3–4 million new cases of infection each year. The risk of HCC is increased 11.5- to 17-fold in HCV-infected subjects (55). HCV is unable to reverse transcribe its RNA and thus to integrate it into the host genome, whereas viral protein expression has a critical role in hepatocarcinogenesis by altering signal transduction pathways (reviewed in ref. 55). Therefore, preventing HCV infection is a key strategy for HCC prevention. The introduction of anti-HCV testing between 1990 and 1992 in developed countries has been associated with a substantial ($>$90%) reduction in cases of posttransfusion hepatitis C (78,79). Other measures to avoid blood contamination in medical settings include 'universal precautions' for blood-borne infections, such as disposal of needles, syringes and any device contaminated by blood or serum, adequate cleansing and sterilization of endoscopic equipment, avoiding multiple use vials for injectables, gloving to handle wounds and blood products, and avoiding transmission to patients from viremic health care workers. Since most new HCV infections in the world are attributable to intravenous drug use, interventions to control this social problem are important in prevention of HCV-related cirrhosis and HCC. Sexual and vertical (mother to baby) transmissions are possible for HCV, but these routes are relatively unimportant in quantitative terms. Apart from safe sex recommendations, there are no other relevant preventive implications. Cesarean section has not been shown to decrease the risk of perinatal transmission nor it is recommended to avoid breastfeeding (80).

Clear evidence exists that antiviral treatment of acute HCV infection reduces the rates of chronic hepatitis C (79,81), and by inference, this would be expected to lower the risk of HCC. Pooling of literature data suggests a slight preventive effect of interferon on HCC development in patients with HCV-related cirrhosis (82,83). Due to anti-necroinflammatory effect and suppression of viral replication, treatment with interferon is estimated to reduce approximately by 50% the annual incidence of HCC in chronic hepatitis C with cirrhotic or precirrhotic liver (82).

In addition, a variety of chemopreventive agents have been assayed in experimental test systems for the prevention of HCC. Some agents, such as glycyrrhizin, ginseng and selenium, were evaluated for the

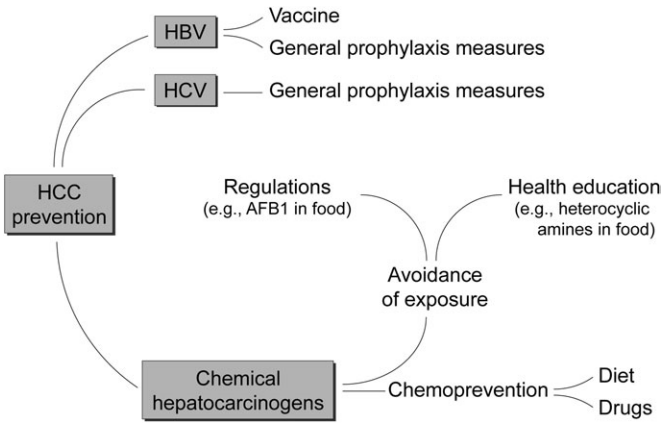

Fig. 2. Co-ordinated strategies aimed at preventing HCC.

ability to decrease the risk of developing HCC in HCV-infected individuals (82).

Attempts to develop an effective vaccine against HCV have failed to date, mainly due to the extreme genetic variability of this virus. Unquestionably, viral diversity and genetic heterogeneity in HCV infection play an essential role in viral immune escape and the development of chronic infection. A central question in HCV vaccine development is whether long lasting, sustained protective immunity against HCV can be achieved. The available evidence indicates that the timing, magnitude and breadth of adaptive immune responses are important. Spontaneous recovery from HCV infection indicates that successful immunity is possible. However, reinfection has been demonstrated to occur in chimpanzee and human studies (84,85). Future developments in the field of therapeutic vaccines will clarify whether a much awaited vaccine against the dreadful long-term consequences of HCV chronic infection will be possible.

HPV-associated cancers

HPV contagiousness is very high, so that barrier measures are not totally protective. Moreover, even non-penetrative modalities of sexual intercourse are considered sufficient for transmission (86). For these reasons, only an effective vaccine against HPV is able to ensure an effective primary prevention of these infections. Two preventative vaccines against HPV have been developed and are currently used in population vaccination programs in many countries. Both of them are obtained by recombinant-DNA techniques and contain the envelope protein L1, which spontaneously reassembles to form virus like particles. The two products are (i) a quadrivalent vaccine against HPV types 16. 18, 6 and 11, adjuvanted with amorphous aluminium salts, and recommended in three doses at 0, 2 and 6 months, and (ii) abivalent vaccine against HPV 16 and 18, adjuvanted with the adjuvant system AS04, a mixture of aluminium salts and monophosphoryl-lipid A, and recommended at 0, 1 and 6 months. Both vaccines are aimed at the prevention of those HPV types that are responsible for ~70% of cervical cancer cases in the world. In addition, the quadrivalent vaccine is intended also for the prevention of genital warts. Both vaccines were studied in large phase 3 clinical trials involving tens of thousands of subjects (87,88). Current HPV vaccines hold great promises also in reducing the burden of HPV-associated non-cervical cancer (89).

A certain degree of cross protection has been demonstrated for both vaccines, so that up to 85% of precancerous lesions can be prevented through vaccination. Protection is demonstrated for several years after vaccination. The relative importance of maintaining a certain (unknown) level of anti-L1 antibodies versus the relevance of immunological memory to ensure long-term protection is still debated. A crucial question is whether we can rely on immunological memory for the required long-term protection after immunization at preadolescent age or, alternatively, if periodical booster doses will have to be envisaged (90).

The chance to control cervical cancer on a global basis will largely depend on the possibility to finance universal vaccination programmes in the female population of all countries in the world, also considering the difficulties to set up screening programmes in the poorest settings. An effort by international agencies and partnerships, such as the Global Alliance for Vaccines and Immunization, to supply HPV vaccines at an agreed low cost or for free will be one of the main challenges for cancer prevention in the near future.

Clearly, even a large-scale use of anti-HPV vaccines needs to be coupled with the secondary prevention of HPV-related cancers.

HIV-associated cancers

Preventing the infection with HIV or, at least, limiting the number of HIV-infected cells and the viral load would greatly contribute also to the reduction of associated cancers (91). AIDS prevention has insofar been based on the detection of infection sources by HIV testing and behavioral measures aimed at controlling HIV transmission via sexual intercourse, blood and other body fluids and perinatal exposure of fetuses and children. General preventive measures mainly consist of the screening on blood transfusions and donated organs by ELISA tests and nucleic-acid based techniques, and of the implementation of universal precautions for the prevention of blood-borne infections. Some studies have also reported a protective effect of circumcision on the chance of transmitting HIV to the sexual partner.

The development of effective vaccines against HIV has been one of the biggest and, to date, unresolved challenges for medical science in the last 25 years, due to the ever changing antigenic profile of the virus and to the inability to identify necessary conserved epitopes for the occurrence of infection. An effective HIV vaccine would need to elicit a broad and long-lasting humoral and cellular immune responses, at both mucosal and systemic level. Some suggestions may be derived from the experience in cats (Feline immunodeficiency virus), where studies on inactivated virus and Feline immunodeficiency virus-infected cell vaccines led to the release of the first licensed vaccine against Feline immunodeficiency virus, in 2002 (92).

Unfortunately, our comprehension of correlates of protection against HIV infection is still poor. Several features have been recognized to be related to resistance to HIV infection and/or disease, namely genetic polymorphism factors (i.e. CCR5 Δ32 homozygosis), innate immunity factors (for instance, enhanced production of interferon-γ by NK cells), adaptive immunity factors (for instance, high level of neutralizing IgA in the genital mucosa, prevalent interleukin (IL)-2 production by CD4 and polyfunctional profile of CD8 T-cells) and major histocompatibility complex haplotypes (B57, B5801 and to a lesser extent B27 are overrepresented in the so-called long-term non-progressors) (93).

Many HIV vaccine candidates have been tested in clinical trials. One of the most recent attempts involved a vaccine made by a mixture of three separate replication-defective adenoviruses expressing the *gag*, *pol* and *nef* genes. Unfortunately, no protective effect was shown in subjects immunized with three doses compared with placebo recipients (94). Another recent study performed in Thailand using a prime-boost approach, involving a basic immunization cycle with four priming injections of a recombinant canarypox vector vaccine (ALVAC-HIV), plus two booster injections of a recombinant glycoprotein 120 subunit vaccine (AIDSVAX B/E), gave a statistically significant efficacy of 31% (95). A possible future approach would be to address viral vulnerabilities at the mucosal portal of entry in the earliest stages of infection that might be most effectively targeted by vaccines and microbicides, thereby preventing acquisition and averting systemic infection, CD4 T-cell depletion and pathologies that otherwise rapidly ensue (96). Recently, it has been demonstrated that an exceptionally broad HIV-1 neutralization can be achieved with individual antibodies targeted to the functionally conserved CD4-binding site (97).

Taken together, all the experiences accumulated to date in the study of vaccines provided no impact on HIV prevention and, as a consequence, on HIV-related cancers. However, the wealth of knowledge on viral features and on innate and adaptive immunity to HIV make us confident on the possibility to find a suitable vaccine candidate in the coming decade.

In addition to the above described measures, aimed at preventing HIV infection, the primary prevention of HIV-associated cancers is also based on the therapy of AIDS, which has greatly improved with the introduction of highly active antiretroviral therapy, mainly based on the use of protease inhibitors. This treatment has been shown to considerably decrease the incidence of HIV-associated Kaposi's sarcoma and non-Hodgkin's lymphoma (98,99). Therefore, almost 30 years after the onset of the AIDS epidemics, there has been a dramatic change of AIDS-related malignancies. Unfortunately, there has been a parallel increase of the so-called non-AIDS defining cancers, the most common of which are Hodgkin's lymphoma, anal cancer, HCC, oral cancer and lung cancer (100,101). It should be noted that, in spite of the promising experimental data regarding their efficacy as cancer chemopreventive agents (102), the protease inhibitors used at high doses in the therapy of AIDS seem to fail in protecting HIV carriers from non-AIDS defining cancers.

Helicobacter pylori-associated cancers

A very broad literature provides evidence that *H.pylori* causes gastric cancer and MALT lymphoma (18,19), to such an extent that gastric cancer has been defined an infectious disease (103). Intriguingly, an inverse relationship has been observed between *H.pylori* infection and incidence of esophageal cancer (18), which is influenced by cyclooxygenase-2 polymorphisms (104). *Helicobacter pylori* infection is an extremely frequent bacterial infection, the stomach of at least half of the world's population, i.e. >3 billion people, being colonized by this bacterium, especially in developing countries, where 80–90% of the population may be carrier after the first 2 decades of life (19). These differences are due to poor socioeconomic status, overcrowded conditions, sanitations problems and household hygiene conditions (105).

Since oral–oral and fecal–oral routes have been postulated to be involved in the transmission of *H.pylori*, the first possibility of preventing the associated stomach cancer consists in avoiding the infection by means of personal hygiene, control of water supply, food quality control and other measures that are usually effective for limiting the spread of infectious diseases through these transmission routes.

In addition, a specific primary prevention approach is provided by the development of vaccines using key bacterial factors, such as urease, vacuolating cytotoxin (vacA), cytotoxin-associated antigen (cagA), the pathogenicity island and neutrophil-activating protein. In their native or recombinant forms, these proteins have been shown to confer protection against infection challenge with *H.pylori* in experimental animal models. Clinical trials in healthy volunteers are in progress (106).

So far, the most obvious strategy for preventing *H.pylori*-associated cancer has been eradication of this bacterium in infected subjects. In fact, *H.pylori* colonization of the stomach rarely resolves spontaneously while it tends to chronicize either in an asymptomatic way or by producing a cascade of events from gastric atrophy to intestinal metaplasia and dysplasia and ultimately to adenocarcinoma. Treatment of *H.pylori* infection is based on the administration of multiple drugs. The triple therapy uses a proton pump inhibitor and the antibiotics clarithromycin and amoxicillin, whereas the quadruple therapy uses a proton pump inhibitor, bismuth, tetracycline and metronidazole (107). Regimens based on levoxacin, rifabutin or furalozidone have also been proposed (108), and sequential therapy is promising (109). Unfortunately, eradication is not always successful, mainly due to lack of compliance and to antibiotic resistance (110). Several intervention trials have demonstrated that *H.pylori* eradication may lead to regression and prevention of progression of precancerous lesions, being most effective before development of atrophic gastritis (111), and a recent meta-analysis concluded that *H.pylori* eradication treatment seems to reduce gastric cancer risk (112). Interestingly, eradication of *H.pylori* leads to regression of primary low grade B-cell gastric lymphoma (113).

Chemoprevention is a further approach to prevent the risk of *H.pylori*-associated cancer. For instance, red wine and green tea were shown to prevent *H.pylori*-induced damage to the gastric epithelium, possibly involving *vacA* inhibition, in a murine model (114). In principle, cyclooxygenase-2 inhibitors and other anti-inflammatory agents would be expected to inhibit *H.pylori*-related gastric carcinogenesis (103). The selective cyclooxygenase-2 inhibitor celecoxib was found to reduce the severity of gastric precancerous lesions following *H.pylori* eradication (115). Celecoxib prevented gastric cancer occurrence by disrupting the progression of intestinal metaplasia to gastric carcinoma through its inhibition of Cdx2 expression in *N*-methyl-*N*-nitrosourea-pretreated *H.pylori*-infected Mongolian gerbils (116). In addition, the anti-inflammatory drugs rebamipide and nimesulide exerted chemopreventive effects in C57BL/6 mice infected with *H.pylori* (117).

Finally, for the primary prevention of *H.pylori*-associated cancers it is important to detect high-risk individuals in the population. The most important *H.pylori* polymorphic genes associated with gastric cancer are *cagA* and *vacA*, whereas human polymorphic genes encode inflammatory cytokines, such as IL-1β, IL-1 receptor β, IL-10 and tumor necrosis factor-α (118). The interplay between bacterial and host gene polymorphisms may explain why gastric cancer only occurs in a small fraction of carriers and perhaps may be useful to detect high-risk individuals (119).

Conclusions

In principle, the fact that certain chronic infections lie at the root of 20% of human cancers is expected to render their primary prevention more practicable. In fact, removal of the etiological agent will result in the control not only of the specific infectious disease but also in the prevention of the associated cancer. In certain prevention programs, such as the anti-HBV vaccination of the population, cancer prevention has been a 'side effect' of an intervention that originally had mainly been addressed to the prevention of a fearful infectious disease. In other cases, such as the anti-HPV vaccination, the intervention program has been launched with the specific objective of preventing the associated cancer rather than the infectious disease, which has poor clinical relevance. Indeed, this is an outstanding breakthrough in cancer prevention strategies. Likewise, the secondary and tertiary prevention of infection-associated cancers may take advantage from the circumstance that microbe-related markers may be detected in the host organism. However, further advances are needed to discover new infection-associated cancers, to elucidate the mechanisms underlying the relationship between microbial or parasitic diseases and cancer and to develop novel strategies that may be applied on a large scale, especially in developing countries, for the prevention of both infectious diseases and cancer.

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