

## Infectious agents and human malignancies

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## 1. ABSTRACT

Cancer has periodically been proposed as transmissible disease in animals and humans, and specific pathogens have long been searched for. Several biomolecular studies, fundamental in understanding cancer pathogenesis, have identified mechanisms directly/indirectly involved in pathogens-related cancer, including 1) oncogene transduction, with introduction of exogenous oncogenic genes; 2) activation of endogenous oncogenes, comprising those from endogenous retroviruses; 3) inactivation of constitutive suppressor genes, with enhanced susceptibility to exogenous oncogenic agents. Further pathogens' indirect role is associated to cancer promotion through inflammation and angiogenesis. The global burden of cancer associated with infectious agents approaches 20% of all malignancies. Most of the common "infectious" cancers occur in developing countries and their "attributable risk" (i.e. the proportion of cancers that would not occur if the agent were removed) is considerable. Although the cancer role of often ubiquitous pathogens, and the molecular mechanisms involved in the infrequent progression of chronic infections to cancers are still often unknown, the identity of the agents and efforts to mitigate their effects can lead to effective cancer prevention and substantive public health benefit.

## 2. INTRODUCTION

Studies on infectious diseases and cancer have been fundamental on cancer pathogenesis and several Nobel prizes have honored research in the field including those to Johannes Andreas Grib Fibiger (1926); Peyton Rous (1966); David Baltimore, Renato Dulbecco and Howard M. Temin (1975); Michael J. Bishop and Harold E. Varmus (1989); Barry J. Marshall and Robin J. Warren (2005). Other landmark studies have been of great relevance for the field leading Harald zur Hausen in 1991 to estimate that a significant fraction of all human cancers worldwide (about 1 in 5 human cancers) are associated with infections due to viruses and microbial agents (1). The pioneeristic work, at the beginning of the XX century, of Fibiger on the role of pathogens in murine stomach cancer resulted in the identification of the *Spiroptera Carcinoma* as the "stomach cancer bacillus" and the Nobel prize award to the Danish scientist in 1926 (2), followed by discoveries in 1910 by Rous of a cell-free transmissible oncogenic pathogen (3), in 1932 by Shope and Hurst of the oncogenic activity of a Papillomavirus in domestic rabbits (4), in 1936 by Bittner of the oncogenic role of mouse mammary virus (5) and in 1951 by Gross of the viral cause of murine leukemias (6). All these observations inspired studies on the role of pathogens in human cancers leading to the identification in

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**Table 1.** List of infectious agents linked to cancer

Agent	Cancer	Reference
Epstein-Barr virus	Burkitt's lymphoma Hodgkin's disease Nasopharyngeal carcinoma	(34), (36)
Human papilloma virus	Carcinoma of the cervix and penis Carcinoma of the head and neck	(1,13,53)
Hepatitis B virus Hepatitis C virus	Hepatocellular carcinoma	(14,47,49)
Human T-cell lymphotropic virus-I (HTLV-I)	Adult T cell leukemia	(18,63)
Helicobacter pylori	Stomach cancer Mucosa-associated lymphoma	(62,65,71)
Kaposi's sarcoma herpes virus (also known as Human herpesvirus 8)	Kaposi's sarcoma Castleman's disease Primary peritoneal lymphoma	(38,72)
Schistosoma haematobium	Squamous carcinoma of the bladder	(63,69)

1964 by Epstein and collaborators of the first association of a virus to human cancer (7) suggested by the observation made by Burkitt in Uganda of a peculiar children lymphoma with a geographic distribution corresponding to rainfall and temperature patterns. Several seroepidemiological studies, particularly in Uganda confirmed the association between EBV and Hodgkin's Lymphoma and few years later the association with nasopharyngeal carcinomas (8).

This discovery, along with the development of model systems in animal and cell culture, led to a major research initiative on the role of viruses in cancer (a partial list in Table 1). The '70s represented a very dynamic period for the viral oncology field with several virus-cancer associations established mainly on the bases of seroepidemiological data (including Herpesviruses, such as HerpesVirus Simplex 2 and cervical cancers (9,10), Human Cytomegalovirus and Kaposi's Sarcoma (11)) to be confirmed or confuted in the following three decades.

Seminal work in the 1970s blazed the trail of the viral etiology of carcinoma of the uterine cervix. Beral first showed that cervical cancer behaved like an STD in 1974 (12), and zur Hausen suggested human papillomavirus as the putative oncovirus (13). It is now indisputable that cervical cancer, cancer of the ano-genital tract, penile cancer, and some oro-pharyngeal cancers are caused by certain strains of HPV.

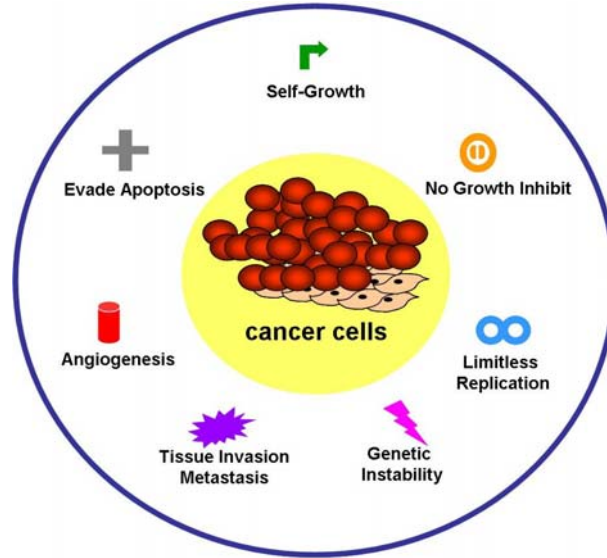
In the same period Vogel *et al.* acquired preliminary data on the role of Hepatitis B in Liver cancer in Uganda (14) and in following studies (15) clear etiological link emerged between hepatitis B virus (HBV) and the hepatocellular carcinoma, later extended also to the hepatitis C virus (HCV) infections. In both cases the virus association has been complicated by the long incubation period, the necessity for intervening chronic inflammation or cirrhosis, and the influence of cofactors such as dietary aflatoxin in the pathogenesis. The HBV vaccine, introduced in the last 15 years, has already demonstrated the potential to lower the risk of hepatocellular carcinoma.

By the end of the '70s no new human tumour viruses had been discovered and interest in tumour virology was waning, shifting towards oncogenes and genetic aspects in cancer. The breakthrough occurred in the early

1980s, when several major discoveries occurred and viruses/pathogens were finally established as the major cause of human cancer. Besides the identification in 1983 of HPV16 from human cancer specimens (16) and the first demonstration in 1985 that persistent HBV infection was strongly associate with liver cancer progression (17), in 1980 the first link between a retrovirus (Human T-cell leukaemia virus, HTLV-I) and a human leukemia was identified (18). The latter success was achieved on the basis of new technologies, developed along with new reagents and tools (including retrovirus-specific reverse transcriptase RT assay) (19), leading to the discovery of the first T-cell mitogenic factor (TGCF) (20), identified as Interleukin-2 (IL-2).

In early '80s were laid also the bases for the discovery of the aetiological agent of Gastric cancer, the second leading cause of cancer death worldwide. The discovery of *H. pylori* as the causative agent of the majority of stomach cancers has enabled an etiological link between microbial and host factors. Similarly, the association of schistosomiasis and carcinoma of the bilharzial bladder also points to chronic inflammation in the carcinogenic process.

Finally, the relevance of the role of infective agents in cancer etiology was busted by the advent of HIV/AIDS epidemic, which in 1981 was heralded by sub-epidemics of Kaposi's sarcoma (KS) and non-Hodgkin lymphoma (NHL), supporting the viral hypothesis and raising suspicions that HIV-induced immune suppression uncovered a viral etiology. Although some lymphomas are linked to Epstein Barr virus and more recently to hepatitis C virus (HCV), KS has long resisted attempts to impugn an infectious etiology. The discovery of Kaposi's sarcoma herpesvirus (KSHV or HHV-8) as the causative microbe opened new avenues of viral oncogenic research. Molecular virology revealed putative oncogenes, host-virus relationship (including latency and the virus receptor), and potential mechanisms of oncogenesis in the endothelial target cells. Seroepidemiology connected areas of high KSHV prevalence with KS and suggested modes of transmission. KS and NHL incidence fell dramatically in populations treated with highly active antiretroviral therapy as a result of improved immune function. But KS remains a major clinical problem in developing countries where both HIV and KSHV are endemic and antiretroviral therapy is



**Figure 1.** The Hallmarks of cancer, modified and reproduced with permission from (24).

not yet available to all. NHL remains a clinical problem in HIV infected patients, although it is an order of magnitude less common than KS and its viral etiology more suspect.

The link between chronic infection and cancer has given insights into cancer biology. An immune response to oncogenic virus would normally be protective and might avert infection and malignant transformation. But perversely, inflammation can be pro-carcinogenic, especially via cytokines mediated by the innate immune response. Thus, transcription factors such as NF- $\kappa$ B and cytokine mediators such as TNF- $\alpha$  and prostaglandins are linked to tumour promotion. A delicate balance exists between the virulence and persistence of the infectious agent and the host immune response. A disturbed equilibrium can initiate malignant transformation, especially in the setting of chronic inflammation. The insights gained by the study of “infectious cancers” can lead to effective prevention efforts on a global scale.

### 2.1. Cancer pathways

The past three decades have greatly accelerated our knowledge of the multi-step molecular events leading to malignancy. The revelation of oncogenes, tumour suppressor genes, and the successful sequencing of the human genome have generated a new paradigm of cancer causation, refining the older dogma of initiation, promotion, and progression. The DNA “blueprint” originally believed to explain much of genetic susceptibility to disease is now known to be vastly more complex. In addition to gene polymorphisms, genetic variation, within and between species, is also the result of a network of epigenetic influences mediated by untranslated interfering RNA (micro RNAs (miRNAs) and short-interfering RNAs (siRNAs) (21,22), methylation, and myriad of interconnecting molecular systems that direct development, differentiation and growth programs. Cellular survival is dependent on the integrity of DNA and the ability of the dividing cell to faithfully replicate and

propagate its genome. Furthermore in pluricellular organisms the “normal”/healthy status is dependent from an equilibrium among the cellular components in each tissue/organ based on several control systems including hormones/growth factors, nutrients supply/angiogenesis, immunity. Alterations of this finely regulated homeostasis can lead to dysplastic/neoplastic conditions characterized mainly by growth-factor-independent autonomous growth, nutrients-independency, and/or immune-escape.

### 2.2. Oncogenesis

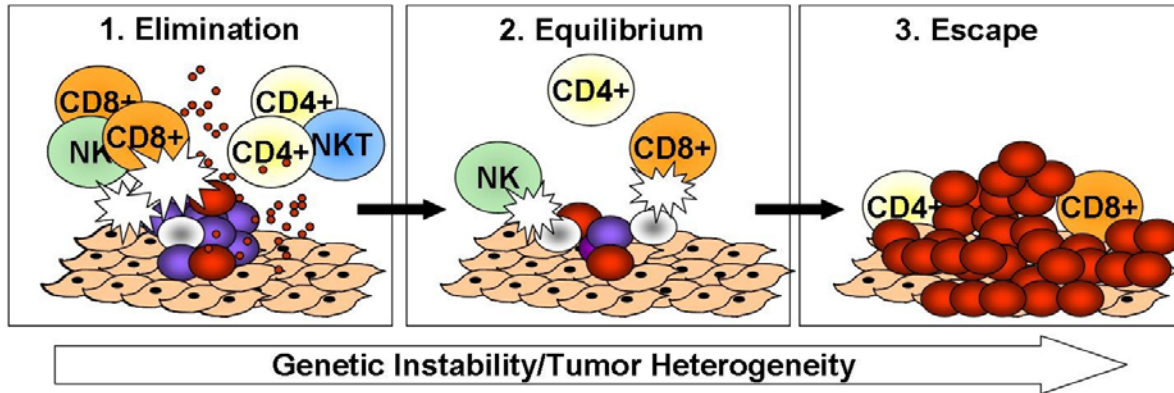
Many studies indicate that cancer develops from a single progenitor “stem” cell whose growth and differentiation program has been corrupted (23). As shown in figure 1, Hanahan and Weinberg (2000) propose that the cellular attributes leading to malignancy follow a set of “rules” (24), namely

1. Acquire mitogenic autonomy
2. Resist exogenous growth-inhibitory signals
3. Evade apoptosis and immune control
4. Undergo immortalization
5. Develop a vascular supply

At the heart of the neoplastic transition is genomic instability, the inability of the cell to recognize and repair DNA damage or to eliminate cells with grossly defective DNA. A mitogenic environment is also a mutagenic environment, and genetic instability is a broad characteristic of malignant cells as they become autonomous. Selection forces inevitably favour survival and spread of cells with a growth advantage.

### 2.3. Cancer and inflammation

Many cancer investigators are studying paracrine effects of tumour formation, and interaction between stroma and epithelium has become a fruitful field of oncogenic research. An inflammatory milieu is in many ways a cancer-favoring environment. Inflammation creates



**Figure 2.** The three Es of cancer immunoeediting, modified and reproduced with permission (73).

free oxygen radicals that are toxic to cells and are highly mutagenic. Invading tumour-associated macrophages and immune cells secrete growth factors, enzymes and cytokines that favour cell proliferation and degradation of the intercellular matrix (25). An inflamed site also encourages angiogenesis as part of the wound healing process. Mouse models that link inflammation and cancer implicate the transcription factor NF $\kappa$ B and the inflammatory mediator tumour necrosis factor- $\alpha$  in tumour progression (26,27).

#### 2.4. Tumour immunity

Another consideration in the neoplastic process is the role of host immunity. A recent synthesis of the field of tumour immunology (28) posits three phases of "immunoeediting" (See figure 2). The earliest phase is the elimination of nascent tumour cells, corresponding to the long-held paradigm of "immune surveillance". A second phase, termed "equilibrium" describes a tumour/immune standoff wherein tumour cells are dormant or slowly evolving, held partially in check by tumour-directed immunity. The third phase, termed "escape", is the result of intrinsic tumour development and the selective pressure of the immune response. Although most evidence for effective tumour immunity is indirect, it is also clear that a "successful" tumour must evade the immune response in order to progress (29).

### 3. INFECTIOUS AGENTS AND CANCER: EVIDENCE FOR CAUSALITY

Impugning an infectious agent as the cause of disease was first codified by Koch in the late-19<sup>th</sup> century, whose "postulates" are learned by every medical student: the organism must be found in diseased tissues; the organism must be grown in pure culture; and the cultured organism must induce the disease experimentally. Today, causality, particularly for cancer diseases has become more complex, as the chain of events leading to disease involves many interacting factors: genetic susceptibility (or resistance); environmental exposures; lifestyle; and even social class. Etiological associations between infectious agents and cancer exemplify the difficulties of causal attribution. First, the agent must be identified in the tumour. Modern molecular biology has eased this task, but multiple

detection methods should be used (e.g. DNA, RNA or protein) to avoid false positives. Evidence for "hit and run" mechanisms, where putative agents cannot be found in the tumour, is weak. Support for a causal association is enhanced by discovery of biological mechanisms (e.g. viral oncogenes) that could transform target cells. Epidemiological evidence estimates the effect size of the infection-cancer association, and prospective studies can show that infection precedes tumour development. Epidemiological studies can also demonstrate a reduction of cancer that may accompany removal of the infectious agent from the environment by hygienic improvement or vaccination. Finally, clinical observation that a tumour will regress following treatment of the agent (sometimes a serendipitous observation) is also a strong evidence of an etiological association (30).

#### 3.1. Epstein Barr virus (EBV)

EBV was the first viral agent to be linked to a human malignancy. Experimental oncogenesis in animals had established that certain viruses could cause cancer, starting with the discovery of Rous sarcoma virus (3,31). But decades of research failed to support a viral etiology of cancer in humans. The discovery of Burkitt's lymphoma in Uganda in 1958 and a description of its geophysical limits to equatorial Africa sparked renewed interest in a viral cause, possibly vectored by mosquitoes. In the 1960s the Henles in Philadelphia and Georg Klein in Stockholm provided more circumstantial links of EBV to Burkitt's lymphoma (32,33), and Burkitt later posited that endemic malaria was an etiological cofactor (34). An important study by de Thè and colleagues established that EBV antibodies in high titre long preceded the development of lymphoma (35).

EBV can immortalize B lymphocytes, an attribute that causes polyclonal proliferation and possibly a neoplastic escape for selected, mutant B cells. Latent membrane protein 1 (LMP1) is an important mediator of proliferation signals, although this protein is not expressed in Burkitt's lymphoma cells. In immune suppressed individuals, EBV may cause a lymphoproliferative syndrome that will progress to malignancy. Such tumours will regress on restoration of immune competence, demonstrating that effective T cell immunity represses

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EBV-induced B cell proliferation. But after decades of research, EBV cannot be impugned as causal, leading one of the experts to say: “There is no satisfactory explanation of how EBV participates in the pathogenesis of Burkitt’s lymphoma” (36).

EBV is also associated with other malignancies, most notably some forms of Hodgkin’s lymphoma and nasopharyngeal cancer (NPC). In the latter condition, endemic in Asian countries, EBV RNA is present in all NPC cells and diagnosis can be made by detection of EBV IgA antibodies (37). EBV is present in nasopharyngeal epithelium and the malignancy is a clonal outgrowth of EBV infected cells, perhaps aided by expression of latent genes (LMP1 and 2) that encourage cell proliferation (36).

### 3.2 Kaposi’s sarcoma herpes virus (KSHV)

KSHV, discovered in 1994 (38), is also known as human herpesvirus 8 (HHV-8). Kaposi’s sarcoma (KS), a rare cutaneous neoplasm, was known mostly in tropical Africa in an “endemic” form; it also occurred in immune suppressed transplant patients, and in older men of eastern European origin (39). The advent of HIV-AIDS was initially characterized by a mini-epidemic of Kaposi’s sarcoma, which behaved epidemiologically as a sexually transmitted disease (40). Like its close gamma herpesvirus cousin EBV, KSHV, also has attributes that could lead to cancer.

A detailed description of the many putative oncogenes carried by KSHV is beyond the scope of this review, but several recently described mechanisms deserve mention. First, KSHV infects endothelial cells, causing them to spindle and elongate, similar to the spindle cells in the classic KS lesions. Two KSHV genes, vFLIP and Kaposin B, are implicated as pro-inflammatory mediators (41). Second, inadequate immune control allows some infected cells to escape latency and enter a lytic cycle, owing to the expression of a viral lytic gene vGPCR that activates growth-promoting genes and paracrine angiogenic factors (42). Third, the restoration of immunity resulting from highly active antiretroviral therapy (HAART) leads to regression of KS lesions. Populations receiving HAART have a low incidence of *de novo* KS, pointing to the anti-KSHV immune response as a key to viral oncogenesis.

KSHV was also linked etiologically to primary effusion lymphoma and multicentric Castleman’s disease, both rare lymphoid tumours. KSHV latency-associated nuclear antigen (LANA) binds the tumour suppressor proteins p53 and pRb, leading to B cell proliferation (43)

In an intriguing new development, latent infection with the murine equivalents of EBV and KSHV is protective against subsequent bacterial pathogens (44). This synergism appears to result from activation of the T cell helper-1 (TH1) arm of the cell-mediated immune system by low-level macrophage production of interferon gamma in herpesvirus latently infected mice but not uninfected littermates. As EBV latent infection is nearly universal in some populations, this unexpected benefit, if true in humans, will change the paradigm of our concept of

“normal” immunity. The observation also offers support for the “hygiene hypothesis” that posits protection from atopy and allergy by frequent infections early in life (45).

### 3.3. Hepatitis B Virus (HBV) and hepatitis C virus (HCV)

Hepatitis B virus, since the first links in Uganda (14) and further high detection in liver cancer patients (46), has been indisputably linked in the causal chain of hepatocellular carcinoma (HCC), especially in Asia and Africa, where carriers of HB antigen (HBAg) have a 100-fold increase in risk (47). Globally, HBV accounts for about 60% of the attributable fraction of HCC (48). Acquired in childhood under crowded and impoverished conditions, most HBV infections are asymptomatic. About 5% become HBV carriers and develop chronic hepatitis that results from a T cell mediated immune response to hepatocytes expressing HBV antigens. In about 20% of carriers, chronic hepatic inflammation progresses to post-necrotic cirrhosis, setting the stage for HCC development. HBV interacts etiologically with dietary carcinogens, especially the genotoxic aflatoxin B1 (AFB1), derived from foods improperly stored and contaminated with *Aspergillus flavus* fungi. Epidemiologic study has unequivocally linked AFB1 to HCC by associating the aflatoxin-induced molecular signature of the tumor suppressor gene p53 (codon 259 mutation) with HBV and HCC. Other cofactors such as alcohol, tobacco, and hepatic iron may play minor etiological roles.

The discovery of HCV (formerly non-A non-B hepatitis virus) and the ability to detect viral footprints quickly led to the expected association with HCC (49). Acquired mainly by parental exposure, HCV predominates in Japan and the West, where the HCC attributable fraction from HCV exposure is estimated at 30% (48). HCV causes chronic hepatitis in up to 85% and about 5-20% will develop chronic liver damage. Interestingly, HCV is also recently linked to a 20-30% excess risk of non-Hodgkin’s lymphoma, particularly splenic marginal-zone lymphoma and Waldenstrom’s macroglobulinemia (50). This latter connection corresponds to established causal role of HCV in cryoglobulinemia, a condition that can evolve into a monoclonal gammopathy.

The molecular pathogenesis of HCC is complex and poorly understood (51). Neither HBV nor HCV contain putative oncogenes. Their effect is more likely mediated indirectly through chronic inflammation, hepatic necrosis, and hepatocyte regeneration. HCC risk in individuals co-infected with HBV and HCV is more than additive, and in all cases exposure to dietary genotoxins such as AFB1 increases risk. The molecular picture is heterogeneous, showing considerable genomic instability and activation of oncogenic pathways such as proliferation, anti-apoptotic, and blockage of differentiation.

It is beyond the scope of this review to discuss prevention, except to point out that development of an effective HBV vaccine led to one of the first “cancer prevention” trials of an infectious agent. Preliminary results from Taiwan, where a large vaccine trial of children was

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begun, show a major decline of HBV carriers (15% to <1%) and a 60% drop in early age HCC (52). An HCV vaccine has not yet been developed. Because HCC is common and carries a high mortality, the major effort should be directed to primary prevention with vaccines, and secondary prevention by screening chronic carriers (alpha-fetoprotein levels and ultrasound, where available, are useful screening tools in high risk populations).

### 3.4. Human papillomavirus (HPV)

HPV since the early studies in the 1970s (13) has been unequivocally linked as the causative agent of carcinoma of the uterine cervix with an attributable fraction of 100% (48). Two subtypes account for more than 70% of the cancers, but 13 other subtypes have also been implicated with lower levels of carcinogenicity (Muñoz *et al.* 2003). Oncogenic HPV subtypes code for protein E6, a potent inhibitor of the tumor suppressor p53 and for protein E7, an inhibitor of the pRb tumor-suppressor protein. These oncoproteins interfere with the integrity of DNA damage repair systems and apoptosis, introducing genomic instability and the potential for cell autonomy (53).

The molecular pathogenesis for cervical cancer is better understood than for other viral-associated cancers. Owing to the preventive success of the PAP smear, we well understand the natural history of cervical cancer as it progresses from early *in situ* epithelial dysplasia (CIN lesions) to invasive carcinoma. The pathogenesis of HPV induced cervical cancer involves a multistep, complex interaction of the host immune response, including innate immunity, chronic inflammation, the expression of viral oncogenes (E6 and E7), the integration of viral DNA into the target cells, and epigenetic changes in dysplastic epithelial lesions (54). The entire process takes 12-15 years on average and the progression risk to invasive neoplasia is related to the HPV type involved in the lesion (55). HPV oncotypes have also been implicated in a proportion of other ano-genital lesions (56-58) and in head and neck cancer (48,53,59).

The advent of an effective HPV vaccine has raised considerable optimism that cervical cancer control, especially in developing countries is at hand. Estimated as the cause of 5.2% of cancers worldwide, a successful vaccine would have an enormous global health benefit. Many questions of efficacy, cost, and logistics remain, however (60,61).

### 3.5 *Helicobacter pylori*

In the past two decades, since the association of a curved bacilli in the stomach of patients with gastritis and peptic ulceration (62), an irrefutable link between *H. pylori* infection and stomach cancer has been established and the worldwide prevalence of gastric cancer tracks with infection rates (63) *H. Pylori* infects 50% of the world's population and causes chronic gastritis. Two distinct types of gastric cancer are recognized. Distal carcinomas of the antrum and pylorus characterize "epidemic" areas of high risk and tend to be of the "intestinal" type pathologically; these well-differentiated cancers are associated with

atrophic gastritis and occur in older people especially men. Tumors of the cardia tend to be poorly differentiated and diffuse, occur in younger people with an equal sex distribution, and are accompanied by gastritis but no atrophy (64,65). Diffuse gastric cancer occurs in a more uniform fashion geographically. Although intuitively *H. Pylori* should be preferentially associated with the intestinal type, the epidemiology links the infection with both types of gastric cancer. As gastritis is common to intestinal and diffuse gastric cancer, the influence of inflammatory mediators, especially from the IL-1 cluster, is the likely carcinogenic pathway (64).

The pathogenesis of *H. pylori* gastric cancer depends on the complex interaction between bacterial virulence, host susceptibility, immune response, and diet. Several *H. pylori* virulence factors are implicated in atrophic gastritis and cancer. Urease permits the organism to neutralize gastric acid. Bacteria flagellae, digestive enzymes and binding proteins enable the organism to invade the mucosa and thrive in a nutrient-rich niche. Two genetic loci, *cagA* and *vacA*, code for virulence factors. *CagA* disorganizes epithelial cell polarity and contributes to pathogenesis of inflammation. *VacA* appears to interfere with the host immune response. Both genes vary considerably and may account in part for the geographic distribution of *H. pylori* associated gastric cancer (65).

*H. pylori* does not act alone, however, and the attributable fraction worldwide is about 75%. A high salt intake and exposure to dietary nitrates (which convert to carcinogenic N-nitroso compounds in an acid environment) are strongly implicated in gastric cancer. High fruit and vegetable intake are protective factors as they contain antioxidants that scavenge nitrites in the stomach (64). Still, the distribution of *H. pylori* and the variations in diet are unlikely to fully explain the geographic variation. Recent evidence shows a bias in the immune response that is conditioned by indigenous infections such as helminthes. In Africa, the adaptive immune response is biased toward TH2 responses, which would avert the host response to *H. pylori* away from gastric atrophy (65). This may explain the "African enigma" wherein *H. pylori* infection is common and gastric cancer rare (65). Clearly, much more study is required to unravel the pathogenesis of gastric cancer. But the etiologic association of a preventable and treatable infection to the number two global cancer killer portends effective prevention strategies.

### 3.6. Human immunodeficiency virus (HIV)

HIV-AIDS, as noted above, was associated with a large excess of non Hodgkin lymphoma and Kaposi's sarcoma, and as the pandemic matured a number of other cancers became associated with HIV (66). The virus, however, does not contain a putative oncogene, and the carcinogenic effect is believed to be an indirect result of immune suppression thus increasing the risk of acquiring and/or activating oncoviruses (67). HIV also activates the immune system as a probable condition for its own survival; chronic inflammation with its attendant cytokines and mediators presumably enhance the carcinogenic milieu.

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HIV is also linked with an excess of Hodgkin's lymphoma, perhaps related to activation of EBV. HIV-AIDS patients treated with HAART experience a 10-fold increased risk of Hodgkin's lymphoma (particularly mixed cellularity type), paradoxically correlated with improved immunity suggesting a role for immunocompetence in the pathogenesis (68). Other cancers associated with HIV such as anogenital malignancy, Kaposi's sarcoma and non-Hodgkin's lymphoma, can be explained by immune suppression and activation of cancer-associated viruses. HIV is also associated with conjunctival squamous carcinoma in equatorial regions, but a putative infectious co-agent has not been detected.

### 3.7. *Schistosoma haematobium*

Carcinoma of the Bilharzial bladder is the commonest cancer in Egypt. *S. haematobium* is endemic in the Nile and its tributaries, and causes chronic cystitis along with altered expression of carcinogen-metabolizing enzymes (69), especially among farmers of the Nile delta (63). The risk of bladder cancer worldwide attributable to *S. haematobium* is 3% (48). As with other chronic inflammatory diseases, the carcinogenic pathway undoubtedly involves inflammatory mediators and carcinogens, possibly nitrites, in the urine. Adequate control of infection should lead to a diminution of bladder cancer prevalence.

### 3.8. Mucosa-associated lymphoid tissue (MALT) lymphoma

MALT lymphomas arise in lymphocyte aggregates associated with chronic inflammation. Histologically MALT lymphomas comprise postgerminal lymphocytes and resemble marginal zone lymphomas (30). MALT lymphomas, though rare, the tumors are informative about pathogenesis because treatment of the underlying infection causes regression. *H. pylori* (gastric MALT), *Campylobacter jejuni* (small intestinal MALT) are good examples of bacterial induced lymphomas that are cured by treatment of the underlying infection (30).

### 3.9. Human T-cell lymphotropic virus (HTLV-1)

This oncogenic virus causes human T cell lymphoma (66). Though rare and mostly confined to endemic areas of southern Japan (70) and the Caribbean, this was first cancer-associated retrovirus to mimic the oncoviruses in animals. (18). The isolation of the human retrovirus analogue HTLV-I, after several decade-long search, was achievable only because of the establishment of a specific reverse transcriptase RT assay (19) and the discovery of the first T-cell mitogenic factor (TGCF) (20) later identified as Interleukin-2 (IL-2). The evidence for causation is compelling, with anti-viral antibodies present in every case, plus clonally integrated virus in the tumour cells (48). The HTLV-1 *tax* gene has transforming properties and can immortalize T cells. As with other viral-associated malignancies, host susceptibility and environmental factors also play roles in leukemogenesis (66). No vaccine is available, but surveillance and heightened awareness in endemic areas can recognize cases in the early stages.

## 4. PERSPECTIVE

This brief overview of oncogenesis in cancers associated with infectious agents reveals the heterogeneity and complexity of the causal pathways. In other papers in this series, we will hear more detail about the transforming mechanisms of these pathogens as well as the role of innate and adaptive immunity. While it is important to learn how infections and inflammation lead to cancer, the recognition of the associated agents in the past four decades has already led to effective public health achievements.

In particular, practical outcomes of this increasing understanding of the mechanism underlying cancer development have been improved diagnosis and identification of people at risk, the possibility to develop specific therapeutic protocols for the respective tumors, and most remarkably for cancer prevention (i.e., the preventive value of early postnatal Hepatitis B vaccination in regions with a high prevalence of Hepatitis B virus persistence). The results achieved thus far are very promising, but a few major obstacles remain to be solved: in particular, the development of efficient immune/pharmacological therapeutic approaches for chronic infections/cancer. Multidisciplinary approaches are needed in order to complement knowledge from several disciplines such as microbiology/virology, immunology, vaccinology, molecular biology, etc. in order to exploit new technologies (antigen identification, gene expression, antigen presentation, adjuvants' discovery and optimization, vaccine formulation, *ex vivo* DC activation, etc.)

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