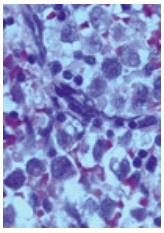

Infections in Oncology

INFECTIOUS CAUSES OF MALIGNANCY

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No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.

Introduction

It has long been believed that cancer arises from genetic changes and that the agents of these changes have roots in toxins or in the environment.[1] In this review, however, we discuss some of the infectious causes of cancer, both suspected and proven. Problems that arise when attempting to associate infection with malignancy include the long incubation periods of many diseases and the many cofactors needed, since malignancies often have more than one cause.[2] Immunosurveillance is known to play a significant role in cancer prevention. For example, renal transplant patients have a 10-fold greater risk of developing anogenital neoplasms.[3] Underscoring the protective role of cellular immunity, lymphocytopenic patients are at a higher risk of malignancy.

In addition to host immune dysfunction, agents of infectious disease produce an immense number of malignancies. Human papilloma virus (HPV) accounts for 500,000 cases of cervical carcinoma each year. Hepatitis B virus (HBV) infection leads to 250,000 cases of hepatoma.[4] In fact, HBV immunization may become, in effect, the first vaccine against cancer.[5] The Table lists the most clearly established and elucidated associations between infectious agents and their corresponding malignancies. Although the leading infectious cause of malignancy is viruses, bacterial infections can also be responsible for development of a cancer. It is postulated that chronic bacterial inflammation produces carcinogenic metabolites.[6] Chronic tuberculous empyemas may occur simultaneously with chest lymphomas,[7,8] and squamous cell carcinomas appear in the chronically draining sinus tracts of osteomyelitis.

Established Associations Between an Infectious Agent and a Malignancy

Pathogen	Malignancy
Helicobacter pylori	Gastric carcinoma
Helicobacter pylori	Mucosal-associated lymphoid tissue
Schistosoma haematobium	Bladder cancer
HTLV-I	Adult T-cell leukemia/lymphoma
HTLV-II	Hairy cell leukemia
HBV	Liver cancer
HHV-8	Kaposi's sarcoma
EBV	Lymphoproliferative disorders
EBV	Nasopharyngeal carcinoma
EBV	Burkitt's lymphoma
HPV	Anogenital carcinoma, cervical cancer

HTLV = human T-cell leukemia/lymphoma virus
HHV = human herpes virus
EBV = Epstein-Barr virus
HBV = hepatitis B virus
HPV = human papilloma virus

Implicating an infectious disease as a cause of malignancy requires careful testing in laboratory animals that are immunosuppressed or at high risk of certain tumors from inbreeding. Several animal models exist as a basis for investigating infectious causes of malignancy. Oncogenic retroviruses infect chickens and cattle,[9] and avian sarcoma and leukemia virus, as well as feline leukemia virus, can simulate HIV in their methods of replication in the host.[2,9] Finally, the pathogenesis of the woodchuck hepatitis virus is comparable to that of the HBV.[2]

Specific Bacterial Causes of Malignancy

The best documented relationship between bacterial infection and malignancy is *Helicobacter pylori* and gastric carcinoma. In early childhood, *H pylori* alters the gastric mucosa at the cellular level resulting in chronic inflammation, permanently reduced acid, and atrophic gastritis. The increased risk of gastric carcinoma in *H pylori* antibody-positive patients after 15 years of infection is eightfold. However, *H pylori* does not directly invade the epithelium and is not found in atrophic foci, but it does promote clonal expansion of selected cells. Inflammatory changes and exposure to carcinogenic cofactors such as nitrosamines and superoxides contribute to the mutagenic effects of the organism.[6]

H pylori is associated with distal (intestinal type) adenocarcinoma of the stomach.[6,10] The greatest risk is for the development of cancers distal to the cardia. Perhaps up to 60% of stomach cancers are attributable to *H pylori* infection.[10] Atrophy increases the relative risk from twofold to ninefold.[6]

H pylori is also associated with the development of low-grade mucosal-associated lymphoid tissue (MALT),[11-13] and antibody positivity carries a sixfold increased risk of developing a b-cell lymphoma.[6] Up to 90% of low-grade MALTs responded to treatment for *H pylori* infection.[12,13]

A rare tumor seen with *H pylori* infection is immunoproliferative small intestinal disease (IPSID). Also known as Mediterranean lymphoma, IPSID regresses when treated with tetracycline. Like gastric lymphomas, there is a greater risk in people with a low socio-economic status who experienced an early childhood diarrheal illness believed to be associated with acute *H pylori* infection.[6]

Other bacteria that may be linked to carcinogenesis are colonic flora such as *Bacteroides* species. *Bacteroides* metabolizes bile salts and, in the presence of exogenous factors, transform them into mutagens. An animal model using *Citrobacter freundii* experimentally produced colonic hyperplasia when these bacteria multiplied in the presence of exogenous factors.[6]

Fungal and Parasitic Causes of Malignancy

The esophageal carcinoma in the Far East is of special interest. The risk of cancer rises with consumption of the bracken fern.[14] It has been postulated that a similar mechanism occurs in geographic localities where consumption of pickled vegetables is high. Molds and fungi in these foods produce copious amounts of the carcinogens known as nitrosamines that may enhance other carcinogens. Organisms implicated include *Fusarium, Alternaria, Geotrichum, Aspergillis, Cladosporium,* and *Penicillium*.

Several flukes and bloodflukes have been linked to certain malignancies through mechanisms similar to that in chronic bacterial inflammation. In a hamster model, the flukes *Opisthorchis* and *Clonorchis* showed increased production of nitric oxide, nitrosamines, superoxide anions, and peroxide.[15] Both *Clonorchis sinensis* and *Opisthorchis viverrini* have been linked to cholangiocarcinoma in their respective hosts.[16] Animal models of *Fasciola hepatica* also demonstrated an enhanced mutagenic effect when infection occurred in the presence of exogenous carcinogens.[17]

Many eggs of schistosomes (blood flukes) do not escape in the feces but form granulomas in the intestine, liver, lung, and urinary bladder. Their egg antigen extracts have transforming carcinogenic properties.[16,17] *Schistosoma haematobium* is linked to squamous cell carcinoma of the bladder and cancer of the venous plexus.[16] *S japonicum* may induce hepatocellular carcinoma.

Viral Causes of Malignancy

An animal model for viral-induced carcinogenesis is Marek's disease of chickens. Infection with this herpes virus results in lymphoma whose prevalence is reduced by vaccination.[4] Genetic alteration of host DNA eventually leads to a loss of control of cellular reproduction, most often via changes in the *myc* and *pRB* genes or their products.[18-20] The *myc* gene was first described in the avian myeloblastosis virus, while the *pRB* gene known from retinoblastoma serves as the regulator of cell entry into DNA synthesis.[20]

Feline leukemia virus (FeLV) is the animal model for HIV-associated carcinogenesis. FeLV is a chronic oncogenic retrovirus associated with both immunosuppression and malignancy.[21] It is often difficult to distinguish between the consequences of immunosuppression and the oncogenic properties of the virus itself. Similar to FeLV, HIV is also linked to non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma, cervical and anorectal carcinomas, Kaposi's sarcoma, and oral cancers.[22]

There appears to be a synergistic relationship between HIV and Epstein-Barr virus (EBV) infection for developing NHL. These lymphomas tend to be either of the large-cell or small-cell noncleaved histotype.[23-25] They are most often of intermediate to high grade and present with B symptoms.[23] The prognosis for persons with NHL who are HIV positive, however, is related more to their CD4 count than to their tumor stage.[23,26] In a patient with AIDS, the risk of developing NHL is 25 to 100 times higher than the general population.[27]

Co-infection with HPV and HIV also greatly predisposes the patient to anogenital carcinomas. They are likely to have greater anaplasia, a greater rate of recurrence, and more extensive disease. Progression of malignancy is again directly related to CD4 count.[3,28]

Two other retroviruses with strong oncogenic properties are the human T-cell leukemic viruses, HTLV-I and HTLV-II. HTLV-I encodes for the oncogene termed *Tox*, which promotes a transforming function by upregulating growth genes.[24] The prevalence of HTLV-1 in Japan is 10% to 15%. It is both horizontally and vertically transmitted. More than 90% of those with adult T-cell leukemia (ATLV) are HTLV-I antibody positive[22]; often they suffer no clinical consequence. The risk of developing ATLV is less than 1% for those infected as adults, rising to 4% under 20 years of age. Of the two aforementioned retroviruses, HTLV-II is the more prevalent type in the United States, notably among intravenous drug users and persons with a history of a sexually transmitted disease.[29] HTLV-II has been linked to hairy-cell leukemia.[22]

Approximately 200 million people worldwide are infected with HBV. Children are much more likely to develop chronic infection than adults at the time of infection.[30] Of those who are HBeAg positive, the vertical transmission rate from mother to child is 90%, whereas the horizontal rate among adults is only 10%.[2] There is an overlap between the geographic distributions of HBV infection and liver carcinoma.[13] Cirrhosis precedes carcinoma in 60% to 90% of cases. The incidence of liver cancer is 474 per 100,000 in the HBsAg-positive population but is only 4.6 per 100,000 in those who are not in this population.[2,31] In a study of HBsAg-negative patients with liver carcinoma, HBV-DNA was identified in 8 of 10 patients with HBcAb and in 6 of 13 without the antibody.[31]

HBV-DNA is incorporated into host DNA at the long arm of chromosome 17. The proposed mechanism of tumorigenesis is incorporation into the host genome, and oncogenic transformation occurs during the HBeAg phase of acute infection.[2,30,31] A gene product of HBV-DNA is antigen X, which serves as a transforming factor inhibiting p53 transcription.[24] Chronic HBV infection confirms a 250-fold risk of developing liver carcinoma.[30]

Like HBV, hepatitis C virus (HCV) is carcinogenic and certain genotypes (1b) tend to behave more aggressively than others.[32] The mechanism for transformation to carcinoma is not clear and, unlike HBV, HCV does not become incorporated into the genome.[20] The risk of diseases in chronic HCV is high: 70% in chronic hepatitis[32,33] and 50% in cirrhosis and liver cancer.[20]

Two recently discovered human herpes viruses (HHVs) have further strengthened the viral oncogenic theory. HHV-6 infects CD4 cells, has a high sero-prevalence rate, has been linked to lymphoproliferative disorders, and has demonstrated its transforming potential in nude mice.[34] HHV-6 has been associated with nodular sclerosing Hodgkin's lymphoma and is present in Reed-Sternburg cells. Its DNA has been isolated from 20% of NHL cells in one series of children and has been implicated in adult T-cell lymphoblastic leukemia.[34]

HHV-8 has been proven to be the causative agent of Kaposi's sarcoma, both the classic AIDS-defining tumor and the Mediterranean Kaposi's sarcoma.[35] It is now understood to be a reactivation of a previous sexually transmitted infection in people who later become immunosuppressed.[36] HHV-8-DNA has also been found in body-cavity-based lymphomas, also referred to as peritoneal-effusion lymphomas.[37]

JC virus (JCV), a polyoma virus, is neurotropic and lymphotropic with primary infection probably occurring in the tonsillar stroma. Its animal model, the hamster polyoma virus, is linked to hematologic malignancies. JCV also has oncogenic properties and has been isolated from astrocytomas, gliomas, and central nervous system lymphomas.[38] JCV has also been associated with acute lymphoblastic leukemia (ALL). The rate of ALL in young children is higher in developed countries than in developing nations. Risk factors

include an urban residence, high socio-economic status, and being first-born. In pregnant women, the protective maternal JCV antibody positivity rate is 90% in Brazil vs 60% in the United States. ALL is twice as prevalent in the United States as in Brazil.[39]

EBV-DNA is found in Reed-Sternberg cells, and there is at least a threefold increased risk of developing Hodgkin's lymphoma in those who are IgG antibody positive. The magnitude of risk correlates with the amount of antibody titer.[2] In developed countries, Hodgkin's lymphoma shows a bimodal distribution of incidence, peaking in children and adults. Elsewhere, there is a single peak early in life, much like that of endemic polio.[40,41]

EBV-DNA has also been detected in NHL and Hodgkin's lymphoma, salivary gland carcinoma, urogenital cancer, thymoma, lymphoblastic lymphoma, T-cell lymphoma, leiomyosarcoma, spindle-cell carcinoma, and leiomyoma, especially in HIV co-infected patients.[24,42-46] The virus has also been found to be related to lymphoproliferative disorders seen in transplant patients. Severity is related to the degree of immunosuppression, being more likely in patients with heart and lung transplants than in those with bone marrow, liver, or kidney grafts.[42] Decreased immune surveillance allows clonal proliferation of EBV-transformed B cells.[47] Viral DNA occurs in poorly differentiated gastric cancer and adenocarcinomas, with lymphocytic infiltrates.[48,49] Patients with a history of chronic pyothorax may be at risk of an EBV-associated large-cell lymphoma.[50]

In some developing countries, IgA antibody levels of anti-EBV are used as a screen for nasopharyngeal carcinoma. In southern China, a positive test indicates a 10-fold risk of disease within 10 years.[2] The risk of tumor progression is inversely proportional to antibody titer.[51] After EBV-RNA is encoded into the preinvasive lesion, EBV-NA1, as well as latent membrane protein (LMP)-1 and -2, is expressed.[24,52] Nuclear antigen EBV-NA2 is not. LMP-1 inhibits terminal differentiation of cells.

In Burkitt's lymphoma, a reciprocal translocation occurs between the c-*myc* oncogene locus on chromosome 8 and another locus on 2, 14, or 22.[24,51] EBV-NA1 on Burkitt's cells is not targeted by cytotoxic T cells.[43] In endemic areas, EBV infection occurs by 2 years of age, and the risk of developing Burkitt's lymphoma within 10 years is considerably raised.[51] This high rate of EBV transmission is thought to be fostered by maternal transmission in prechewed food.[2] Co-infection with falciparum malaria and EBV may be linked to subsequent development of Burkitt's lymphoma.[24] In endemic areas, the rate of EBV antibody-positive patients who also have Burkitt's lymphoma is much higher than among those who have lymphoma and who are EBV negative. A prospective study revealed that the risk of developing lymphoma correlated with the titer of IgG antibody to viral capsid antigen.[2]

More than 90 types of HPV are known to infect genital and nongenital skin and mucosa.[53,54] In one study,[51] a majority of genital warts were HPV-DNA positive, and HPV was type-specific for carcinomas and for stage of carcinoma intraepithelial neoplasia (CIN) lesions. Type 16 is frequently seen in CIN II and III and in cervical cancer.[55] Type 18 is less often found in CIN II and III.[55,56] Although there is a geographic variation in the frequency of HPV types, 16 and 18 are most often linked to malignancy. A variety of types are common in high-grade CIN lesions: 16, 18, 31, 33, 35, 45, 51, 52, 56, 58, and 61.[57] Infection with HPV leads to cervical carcinoma, with type 16-DNA found in 60% of cancers and type 18-DNA found in 20%.[51] Adenocarcinoma accounts for only 12% of cervical cancers, but HPV-DNA is present in more than 70% of these lesions.[58] In patients with HPV-associated condylomas, the risk of malignancy is elevated fourfold in vulvar cancers, twofold in cervical cancers, and eightfold in anal cancers. There is also a greater than twofold risk of developing a CIN lesion. Vulvar and CIN III lesions typically occur within one year, while cervical cancers appear later.[59] The cumulative risk of developing CIN within two years of infection is 28%, increasing 11-fold when the HPV is either type 16 or 18.[56]

Infection of epithelial cells occurs when the HPV binds to the undifferentiated cell, perhaps via the basal keratinocyte receptor.[53,60] Benign lesions have extra-chromosomal DNA, and only malignant lesions are found to have integrated DNA.[56] Viral proteins E6 and E7 dampen the apoptotic response of cells whose DNA has been damaged and promote cell immortality, along with the genome of certain types of HPV, such as 16.[24,56]

The E6 complex binds to the p53 gene product that originates from chromosome 17. The result is a ubiquitin complex that allows protease degradation.[53,61] Loss of p53 regulation results in cell transformation and allows for entry into cell replication despite DNA damage.[56] The cell becomes unable to upregulate p53 gene expression and enters into the G_1-S cycle. The E7 protein binds and inactivates the pRB (retinoblastoma tumor-suppression) product.[19] E7 upregulates transcription of growth-related proteins and cyclins, which also controls entry into the G_1-S cell replication cycle.[53]

Li-Fraumeni's syndrome is a disorder related to a mutant p53 gene. Patients with this syndrome have a high propensity for malignancy.[56] Affinity for p53 and pRB products by E6 and E7 proteins varies proportionately to the oncogenic propensity of the HPV type.[56,62] Another factor that contributes to tumorigenesis is immunosurveillance. MHC-I antigens are downregulated in cervical CIN lesions, most often seen in types 16, 18, 31, and 33.[63]

Another HPV-associated malignancy is demonstrated by the increase in skin cancers in renal transplant patients.[53,64] In some high-risk areas, there is an association between HPV infection and esophageal carcinoma, especially type 16.[65,66] The rate of tonsillar carcinoma is also higher in those who are HPV positive, and these tumors tend to be larger with more lymphatic metastasis, but there is a difference in survival.[67,68] In one study, a worse prognosis was seen in HPV-negative tumors, and the p53 mutation was more frequent in tobacco users.[69,70] HPV-positive patients with tonsillar carcinoma are typically younger, have more advanced disease, and use tobacco less frequently.[70] The most common types seen in oral carcinomas are 6, 11,16, and 18, with 6 and 11 strongly linked to papillomas.[71] HPV has also been encountered in verrucous and conjunctival carcinomas.[72,73]

HPV types 16 and 18 are found in penile carcinomas, 18 being the more common.[51,74] Type 16 also has been seen in Bowen's disease and has been linked to anal carcinomas.[51] The incidence of anal cancer has increased in both men and women with a history of receptive anal intercourse, particularly those who have had previous sexually transmitted diseases, have had multiple partners, are single, or live in an urban area. In one series, 84% of these lesions were HPV-DNA positive.[75] HPV-DNA has been seen in papillary tumors of renal cell carcinomas.[76] In several series, HPV types 16 and 18 were found in more than 60% of prostate cancer biopsies but were absent in benign lesions.[77-79]

Conclusions

Based on this summary, one can conclude that infectious agents may play a greater role in contributing to deaths in countries where rates of mortality due to malignancy exceed those of infection. Bacteria, molds, and similar pathogens display oncogenic potential because of the milieu that they create in states of chronic inflammation. Viral agents also share among themselves a common mechanism of tumorigenesis through cell transformation, via either DNA integration or cellular-DNA alteration of growth regulator genes. Substantial evidence exists for the role of infectious agents in tumorigenesis; however, it is often difficult to prove, given the ubiquitous nature of these infections and because transformation of a normal cell to a malignant one is frequently a multiple-step process.

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