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Chronic Inflammation: A Common and Important Factor in the Pathogenesis of Neoplasia

David Schottenfeld, MD, MSc; Jennifer Beebe-Dimmer, PhD, MPH

ABSTRACT A causal link between chronic inflammation and carcinogenesis is explored by reviewing illustrative examples of specific cancers and causal agents and mechanisms. The causal agents or pathologic conditions include microbial agents, gastroesophageal reflux, chronic cholecystitis and cholelithiasis, inflammatory bowel disease, and specific agents that cause chronic obstructive or diffuse interstitial lung disease. The proportion of total cancer deaths attributable to infectious agents is estimated to be about 20% to 25% in developing countries and 7% to 10% in more industrialized countries. Recurrent or persistent inflammation may induce, promote, or influence susceptibility to carcinogenesis by causing DNA damage, inciting tissue reparative proliferation, and/or creating a stromal "soil" that is enriched with cytokines and growth factors. Future research on the complex cascade of cellular and humoral factors participating in the chronic inflammatory process will further understanding of the pathogenesis of various cancers and potentially provide a rationale for targeted chemopreventive interventions. (*CA Cancer J Clin* 2006;56:69-83.) © American Cancer Society, Inc., 2006.

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INTRODUCTION

In 1863, Virchow hypothesized that malignant neoplasms occurred at sites of chronic inflammation. Virchow reasoned that various "irritants" caused tissue injury, inflammation, and increased cell proliferation.^{1,2} Inflammation involves a complex reaction to microbial, chemical, or physical agents in vascularized tissue resulting in the influx of circulating leukocytes, connective tissue cells, and extracellular constituents consisting of fibrous proteins (collagen, elastin) and glycoproteins (fibronectin, laminin, and proteoglycans). Chronic inflammation may develop from unresolved symptomatic acute inflammation or may evolve insidiously over a period of months without apparent acute onset of clinical manifestations. Histopathologic features of chronic inflammation include the predominance of macrophages and lymphocytes, proliferation of nurturing structurally heterogeneous and hyperpermeable small blood vessels, fibrosis, and necrosis. Activated macrophages and lymphocytes are interactive in releasing inflammatory mediators or cytokines that amplify immune reactivity. Cytokines represent a family of biologic response modifiers including interleukins, chemokines, interferons, growth factors, and leukocyte colony-stimulating factors. The cytokines are secreted by leukocytes, connective tissue cells, and endothelial cells. Chemokines consist of 8- to 10-kD proteins that stimulate leukocyte recruitment and migration as part of the host response to antigenic insults. In chronic inflammation, the protracted inflammatory response is often accompanied simultaneously by tissue destruction and repair.

Dvorak noted similarities and differences between physiologic wound healing and mechanisms involved in the pathologic generation of supporting connective tissue (stroma) that sustains neoplastic cell proliferation and invasion. Dvorak referred to tumors as "wounds that do not heal."^{3,4} The infiltration of leukocytes in neoplastic tissue may be viewed as an antitumor response; however, there is compelling evidence that the infiltrate of activated macrophages and lymphocytes recruited from the microcirculation is a major source of "proinflammatory cytokines," growth factors, and angiogenic factors. The extent of the leukocyte infiltration in solid tumors is controlled in part

by the local production of chemokines by both neoplastic cells and stromal cells. The network of cytokines, chemokines, and growth factors interact with specific cell surface receptors that signal target genes involved in cell proliferation and influence tumor cell survival, neoangiogenesis, and migration of tumor cells into the stromal matrix.

Chronic inflammation and the metabolic products of phagocytosis are often accompanied by the excessive formation of reactive oxygen and nitrogen species that are potentially damaging to DNA, lipoproteins, and cell membranes. Inflammatory cells also release metabolites of arachidonic acid, or eicosanoids, including prostanoids or prostaglandins and leukotrienes. The cyclo-oxygenases are key enzymes that control rate-limiting steps in prostaglandin synthesis. The expression of the isoform COX-2 is induced by inflammatory and neoplastic cells, and metabolites produced by the action of COX-2 on arachidonic acid have been shown to impact various carcinogenic pathways. The neoplastic transformation of proliferating stem cells and subsequent tumor invasion may require a microenvironment of activated inflammatory cells and stromal cell elements.^{4–8} In this review, we identify specific cancers and causal agents and mechanisms in which there is an apparent association with chronic inflammation (Table 1).

MICROBIAL AGENTS, CHRONIC INFECTIONS, AND HUMAN CARCINOGENESIS

Populations in developing countries are disproportionately susceptible to cancers caused by infectious agents. These organ sites and associated pathogens include uterine cervix (human papillomavirus [HPV]), liver (hepatitis B virus [HBV] and hepatitis C virus [HCV]), stomach (*Helicobacter pylori* [*H pylori*]), lymphoid tissues (Epstein-Barr virus [EBV]), nasopharynx (EBV), urinary bladder (*Schistosoma hematobium*), and biliary tract (*Opisthorchis viverrini*, *Clonorchis sinensis*). The public health impact of these infections is substantial. The proportion of cancer deaths attributable to infectious agents has been estimated to range

from 20% to 25% in developing countries and 7% to 10% in more industrialized countries.⁹ The oncogenic actions of viral, bacterial, and parasitic agents may be mediated through autocrine and paracrine signals associated with chronic inflammation or by host somatic cell events influenced by the microbial genome. Each infectious agent has the capacity to persist in the host if not cleared by an effective immune response.¹⁰ Patients with human immunodeficiency virus (HIV) infection, in which there is a dysfunctional immune system, are likely to develop a neoplasm of lymphatic tissue presumably due to the activation of latent Epstein-Barr viral infection, Kaposi sarcoma due to human herpes virus 8, or a neoplasm of the anogenital tract due to human papillomavirus infection. Persistent infections by DNA viruses such as the HPV, EBV, HBV, and Kaposi sarcoma herpes virus (KSHV) have been implicated in human carcinogenesis. The genomes of oncogenic DNA viruses integrate into and form stable associations with the host cell genome. A key to the understanding of the oncogenic potential of infection with a DNA virus resides in the elucidation of the biology of persistent infection within a target tissue. Infection alone is not a sufficient cause of neoplastic transformation unless accompanied by additional somatic mutations and epigenetic events facilitated by exposures to other environmental cofactors and altered immune mechanisms.

Hepatitis Viruses

Chronic infection with HBV or HCV is causally associated with more than 80% of the global incidence of hepatocellular carcinoma. Of the estimated 50 million new cases of HBV infection diagnosed globally per year, 5% to 10% of adults and up to 90% of infants born to infected mothers will become chronically infected. Of the more than 350 million who are chronically infected worldwide, 75% are in China and Southeast Asia, where HBV is the leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. HBV, a double-shelled enveloped DNA virus belonging to the family *Hepadnaviridae*, is transmitted by sexual

TABLE 1 Chronic Inflammation and Human Cancer

Causal Mechanisms	Types of Cancer
<i>Helicobacter pylori</i> and chronic gastritis	Adenocarcinoma of stomach
Epstein-Barr virus	B-cell lymphoma Non-Hodgkin lymphoma Hodgkin lymphoma
Human papillomavirus	Nasopharyngeal carcinoma Anogenital carcinoma Oropharyngeal carcinoma
Hepatitis B or C virus	Hepatocellular carcinoma
HIV/AIDS	Non-Hodgkin lymphoma Kaposi sarcoma
Liver flukes (eg, <i>Clonorchis sinensis</i>)	Cholangiocarcinoma
<i>Schistosoma haematobium</i>	Squamous carcinoma of urinary bladder
Gastroesophageal reflux	Adenocarcinoma of the distal esophagus and gastric cardia
Ulcerative colitis	Adenocarcinoma of the large intestine
Crohn granulomatous colitis	Adenocarcinoma of the large intestine
Chronic obstructive lung disease	Carcinoma of the lung
Chronic lung infections	Carcinoma of the lung
Chronic diffuse infiltrative lung diseases (eg, asbestosis, silicosis)	Carcinoma of the lung
Chronic cholecystitis	Gallbladder carcinoma
Inflammatory atrophy of prostate	Prostate carcinoma

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contact, percutaneously or parenterally as in intravenous drug use, or perinatally from the infected mother to the infant. An estimated 0.33% of the US population are HBV chronic carriers, as evidenced by antigenemia for more than 6 months. High incidence rates of hepatocellular carcinoma (HCC) are evident in Southeast Asia and sub-Saharan Africa, and low rates are evident in the United States and Europe. The estimated population attributable risk percent of the burden of HBV-associated liver cancer varies from 65% to 70% in China and Africa to less than 10% in North America and Australia. The cumulative lifetime risk of HCC in those who are chronically infected is estimated to be 10% to 25%. The latent period from the onset of infection to the diagnosis of HCC may range from 20 to 50 years.¹¹⁻¹³

The increased risk of neoplasia or cirrhosis will be influenced by onset of persistent infection in infancy or early childhood, HBV genotype, or viral load as measured by plasma HBV DNA levels or hepatitis B early antigen. Additional risk factors include immune suppression, coinfection with HCV or HIV, chronic ethyl alcohol exposure, exposure to the aflatoxin of the *Aspergillus* fungus, acquired or inherited iron storage disease, and exposure to tobacco smoke.^{14,15} Aflatoxin hepatotoxicity is associ-

ated with a "molecular signature," namely a G:C to T:A transversion in codon 259 of the *TP53* gene.¹⁶ Cytotoxic T-lymphocytes and cytokines interact with infected hepatocytes, generating recurring cycles of cellular injury, apoptosis, necrosis, and regeneration. The HBV DNA integrates randomly into the host cell genome, and the malignant tumors are clonal with respect to these insertions. There is no consistent pattern of HBV insertion in proximity to a known proto-oncogene. Augmented proliferation of infected hepatocytes triggers genetic instability. The inflammatory process is associated with the local production of oxygen-reactive species that may induce strand breaks in DNA and facilitate integration of HBV DNA. HBV encodes a regulatory element, HBx protein, which disrupts normal mitotic activity in infected cells by augmenting the insulin-like growth factors and receptors network, and by interfering with p53 cell-growth modulating actions. Thus, liver injury due to HBV infection is mediated by both viral and host factors.¹⁷⁻¹⁹

In 1987, the plasma-derived HBV vaccine prepared from healthy carriers was supplanted by recombinant DNA vaccines. In 1992, the World Health Organization (WHO) declared a 5-year goal of universal infant or childhood

HBV immunization. Currently, about two-thirds of the WHO member nations have infant or childhood HBV immunization programs. Based on studies in Taiwan, China, and Africa, it has been projected that the prevalence of chronic HBV infection will be reduced from between 8% and 20% to less than 2%, with a consequential reduction in hepatocellular carcinoma incidence of at least 50%.^{20–22}

In contrast to HBV, HCV is an RNA virus (*Flaviviridae* family) transmitted predominantly by the parenteral route. More than 60% of cases in the United States occur in drug users from contaminated needles and syringes, 15% to 20% from multiple sexual contacts, and 5% from infected mothers to their infants.²³ Population-based studies from the Centers for Disease Control and Prevention indicated that 40% of new cases of chronic liver disease in the United States are due to persistent HCV infection, resulting in 8,000 to 10,000 deaths per year.²⁴ HCV necroinflammatory disease occurs in 55% to 85% of cases after the acute infection. Among these cases, 30% to 50% develop cirrhosis or fibrosis of the hepatic parenchyma resulting in nodule formation. Hepatic cellular proliferation is induced by cytokines, notably platelet-derived growth factor, whereas fibrogenesis is stimulated by transforming growth factor beta. A mechanism for viral persistence appears to be the ability of the virus to mutate and escape host immune mechanisms. After a period of 20 to 30 years from onset of infection, 2% to 4% of those with chronic liver disease develop hepatocellular carcinoma. The rate of progression of chronic liver disease among HCV-infected individuals is increased in males and patients with older age at initial infection (in contrast to HBV), coinfections with HBV or HIV, immunosuppression, and regular use of ethyl alcohol.^{25–28}

The goals of treatment of persistent HBV or HCV infection would be to prevent long-term complications of cirrhosis or hepatocellular carcinoma, and to reduce the number of chronic carriers who would serve as a reservoir of viral transmission. Treatment with long-acting interferon-alfa bound to polyethylene glycol (ie, “pegylated interferon”), either as monotherapy or in combination with a nucleoside

analog (eg, lamivudine, adenovir), has resulted in sustained suppression of viral replication in 30% to 40% of patients infected with HBV and in 40% to 80% of patients infected with HCV. Suppression of viral replication decreases risk of integration of the viral genome into host DNA. Long-term follow up in randomized controlled clinical trials will be required to demonstrate the extent of reduction in risk of hepatocellular carcinoma in patients who are responsive to viral eradication therapy.²⁸

HPV

Specific subtypes of HPV infection are potentially oncogenic in the uterine cervix, vagina, vulva, anus, penis, skin, and oropharynx.^{29–32} In general, HPV infects the germinal layer of dividing basal cells of an epithelial surface. Viral replication and the production of infectious virions proceed in parallel with squamous epithelial differentiation. Worldwide, invasive cancer of the uterine cervix is the second most common cancer registered in women. In reviewing the pathogenesis of cervical cancer, the morphology, epidemiology, and molecular biology may be distinguished in relation to persistent infection, intraepithelial neoplasia, and invasive cancer. The cytopathologic gradient from infection to intraepithelial neoplasia is characterized by increasing nuclear atypia and disordered epithelial differentiation, but without penetration through the basement membrane.

The major subtypes of HPV in cervical intraepithelial neoplasia and invasive cancer are 16 and 18, which account for more than 70% of cases throughout the world. Other oncogenic subtypes include HPV 26, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, and 82. Molecular oncogenic mechanisms involve HPV oncoproteins disabling host tumor suppressor proteins, causing abnormalities in mitotic replication that result in progressive allelic imbalances, and upregulating telomerase that disrupts physiologic senescence of cells. The E6 and E7 oncoproteins are the main transforming genes of oncogenic strains. The product of the E7 gene acts primarily by binding to and inactivating the retinoblastoma (Rb) tumor suppressor gene product. The E6 protein of

oncogenic types binds to and inactivates the TP53 tumor suppressor gene product. Variations in binding efficacy influence oncogenic potential. The pathogenesis of a continuum of different grades of intraepithelial neoplasia, carcinoma in situ, and invasive carcinoma reflects the dynamics of viral persistence and genomic integration, exposures to additional environmental cofactors, host immune responses, and cumulative somatic genetic events.³³⁻³⁵

Sexually transmitted HPV infection is a necessary causal factor for virtually all cases of intraepithelial neoplasia and invasive cancer of the cervix throughout the world. In most instances, however, genital HPV infection is transient or intermittent. The prevalence is highest among young women soon after the onset of sexual activity and then diminishes gradually with age. Persistence of infection increases the probability of cervical cancer after a prolonged latency interval. The integrity of cell-mediated immune responses to HPV is an important factor in viral clearance or persistence. Epidemiologic studies in HPV-infected women have provided important clues concerning a spectrum of cofactors that enhance HPV tumorigenesis. Established cofactors for squamous cell carcinoma include cigarette smoking (ie, risk is higher in current than in former smokers, and increases with amount smoked and duration of smoking), multiparity and prolonged use of oral contraceptives, and sexually transmitted microbial agents. Hormonal factors, including hormone replacement therapy, and increased body mass index appear to be associated with increased risk of cervical adenocarcinoma. HIV infection and immunosuppression related to organ transplantation are associated with increased risk of cervical dysplasia and carcinoma in situ in HPV-infected women.³⁶⁻³⁸ Presumably, infectious, chemical, and hormonal agents serve as cofactors by influencing acquisition and persistence of HPV infection.

A series of relatively recent publications have suggested that other sexually transmitted viral or bacterial agents may serve as cofactors in HPV-infected women with cervical neoplasia. The putative agents include herpes simplex virus (HSV) 2 and *Chlamydia trachomatis*. *C. tra-*

chomatis and HSV-2 infections are often associated with an intense chronic inflammatory response and microulcerations in the cervical epithelium.³⁹⁻⁴¹ Similarly, in penile cancer, ulcerative infections of syphilis or chancroid, phimosis associated with balanoposthitis, and lichen sclerosus chronic dermatitis potentiate the risk of neoplasia in HPV-infected men.^{42,43}

EBV

More than 90% of the adult world population has been infected in childhood or in early adult life with EBV. EBV, a herpes DNA virus, has been implicated in the pathogenesis of Hodgkin disease and non-Hodgkin Lymphoma, including endemic Burkitt lymphoma, B-cell Burkitt-like or immunoblastic lymphoma in HIV patients or following organ transplantation, and nasopharyngeal carcinoma. EBV plays a central role in the pathogenesis of perhaps up to 50% of patients with Hodgkin disease (HD). EBV positivity in HD tumor cells will vary by histopathology, age at diagnosis, sex, socioeconomic status, and geographic area. EBV positivity is more commonly associated with the mixed cellularity and lymphocyte depletion subtypes than with the nodular sclerosing subtype of HD.⁴⁴⁻⁴⁷

Among persons in the United States and most parts of Europe and Israel, approximately 40% to 50% of HD cases contain EBV-positive Reed-Sternberg neoplastic cells. The percentage of EBV-positive cells appears to be even more frequent in pediatric cases from less developed countries in Central and South America. Infectious mononucleosis, a self-limited lymphoproliferative disease caused by EBV, is associated with an increased risk of EBV-positive HD in young adults; the median induction-latency interval between the diagnosis of infectious mononucleosis and the diagnosis of EBV-positive HD in young adults was estimated to be between 4 and 5 years, although the risk may continue to be elevated for several decades. EBV may persist in a latent state, residing episomally in B-lymphocytes throughout adult life.⁴⁸⁻⁵¹

The neoplastic cell of HD is the multinucleated or multilobulated Reed-Sternberg cell, a germinal center or postgerminal center B-cell. The studies of clonal origin indicate that EBV infection precedes expansion of the tumor cell population. Reed-Sternberg cells express high levels of a transforming EBV viral protein, latent membrane protein-1. Reed-Sternberg cells generally account for 1% of cells in tumor tissue, in which the cellular infiltrate is composed mainly of T-cells, B-cells, macrophages, eosinophils, and plasma cells. Although the nonneoplastic cellular infiltrate may represent in part an inflammatory response to a foreign antigen, there is demonstrable evidence that a substantial fraction of inflammatory cells are actively attracted by chemokines and cytokines produced by the neoplastic cells. The Reed-Sternberg cells attract CD4 T-helper cells by secretion of a cytokine normally expressed by dendritic cells. High levels of proinflammatory cytokines, chemokines, and their receptors expressed in HD tissue act as autocrine/paracrine growth factors that sustain clonal expansion of Reed-Sternberg cells. In contrast to the oncogenic action of human papillomaviruses, there is no evidence that host tumor suppressor genes are targeted for inactivation by EBV.^{48,52,53}

H Pylori

H pylori is a gram-negative multiflagellate spiral bacterium that colonizes the luminal surface of the corpus and antrum in the gastric epithelium. Its ability to survive in the acidic environment of the stomach is due to its capacity to penetrate the viscous mucous layer, to adhere to epithelial cells, and to increase the pH in the microenvironment of the gastric niche by secreting urease and thereby releasing ammonia and bicarbonate. *H pylori* is genetically diverse with strains subdivided by their expression of the cytotoxin-associated gene A (cag A) and vacuolating cytotoxin A.^{54,55}

H pylori has been identified as a major cause of multifocal atrophic gastritis, duodenal and gastric ulcer, and adenocarcinoma of the stomach.^{56,57} Stomach cancer is the second leading cause of cancer mortality in the world, accounting for

12% of cancer deaths. Although age-standardized incidence and mortality rates have been declining over the past 25 years even in high-risk countries, stomach cancer accounts for a substantial proportion of cases in Japan, China, Korea, Eastern Europe, and the Andean regions of South America. A meta-analysis of 14 case-control and five cohort studies concluded that persistent *H pylori* infection was associated with approximately a two-fold increase in risk of stomach cancer (odds ratio, 1.92; 95% confidence interval, 1.32 to 2.78).⁵⁸ Critical events in the multistep pathogenesis of adenocarcinoma of the stomach consist of superficial gastritis distal to the cardia, chronic gastritis with multifocal atrophic areas, intestinal metaplasia, dysplasia, neoplastic transformation, and invasive carcinoma. Intestinal metaplasia may first appear in the second decade of life in high-risk populations. Replacement of the oxyntic (parietal cell) mucosa in the corpus and antrum by intestinal or enterocolonic metaplastic cells is accompanied by increasing intragastric pH and a microenvironment favoring bacterial colonization and the generation of genotoxic nitrosamines. *H pylori* evokes an inflammatory reaction in the mucosa by producing chemotactic factors that attract neutrophils, mononuclear cells, and proinflammatory cytokines, and reactive free radicals that may energize nitrosative deamination of DNA.

The marked geographical variations in gastric cancer incidence can be explained in part by differences in prevalence of cag A subtypes of *H pylori*. As determined by antibody surveys in high-risk populations as in China, Japan, and countries in South America, the prevalence of *H pylori* may approximate 75%, compared with about 40% or less in developed nations. *H pylori* is acquired early in life and is observed most commonly in populations of low socioeconomic status who live in crowded households under poor hygienic conditions and suboptimal nutrition. The fact that only a small percentage of infected individuals develop stomach cancer underscores the importance of other environmental and host cofactors in pathogenesis. Of further interest is the global decline in stomach cancer incidence, about 10% to 20% per decade, that is attributed to changing living standards, enhanced availability of fresh vegetables

and fruits, sources of antioxidants, and greater availability of antibiotics.⁵⁹⁻⁶²

Another instructive example of the oncogenic effects of *H pylori* colonization is the association with B-cell lymphomas in mucosa-associated lymphoid tissue (MALT). MALT B-cell lymphomas have been observed in the stomach (about 70% of the total), small intestine, lung, salivary gland, skin, and ocular adnexal tissues (eg, conjunctiva, lacrimal gland). Although *H pylori* is the apparent cause of gastric MALT lymphoma, *Campylobacter jejuni* in the small intestine and *Chlamydia psittaci* in ocular adnexal tissues are linked with B-cell lymphomas in these anatomic areas. Low-grade MALT lymphomas result from aberrant interactions between bacterial antigens, host autoantigens, and host T-cells, resulting in a polyclonal expansion of B-lymphocytes.

The molecular pathogenesis of B-cell lymphomas encompasses translocations in immunoglobulin genes and somatic mutations in genes, such as *BCL-6*, which are critical to B-cell development.⁶³⁻⁶⁵

In contrast to Peyer's patches in the ileum, the gastric mucosa is normally devoid of organized mucosa-associated lymphoid tissue. The immune response to *H pylori* is manifested by a follicular gastritis, namely the accumulation of organized follicular lymphoid tissue accompanied by an infiltration of activated neutrophils, lymphocytes, and plasma cells. Low-grade MALT lymphomas originate from a marginal zone B-cell population. Neoplastic transformation is signaled by genetic events that induce excessive lymphocyte proliferation and defective apoptosis. The most common translocations in MALT lymphomas of the stomach corpus or antrum, namely t(1;14) (p22;q32) or t(11;18) (q21;q21), result in overexpression of the nuclear factor-kappa B signaling pathway. Tumor genomic instability is often accompanied by trisomies in chromosomes 3, 12, and 18, and high-grade treatment-refractory tumors that exhibit inactivation of *TP53* and *CDKN2A* tumor-suppressor genes. The low-grade superficial neoplastic lesions regress when the bacterial infection is eradicated after 7 to 14 days of treatment with a combination of antibiotics and a proton-pump inhibitor, omepra-

zole. This has been accomplished in most instances (about 75%) underscoring the importance of bacterial colonization, tumor genomics, and host immunity.⁶⁶

GASTROESOPHAGEAL REFLUX

Intriguing epidemiologic features of esophageal cancer are its geographic, anatomic, and morphologic variability. The global pattern resembles a mosaic of contrasting incidence rates and sex ratios, which appear to reflect a complex of environmental factors intimately correlated with sociocultural factors and ethnic characteristics. In most parts of the world, incidence rates per 100,000 for esophageal cancer, including the major histologic subtypes, are around 2.5 to 5.0 for males and 1.5 to 2.5 for females, but they may exceed 100.0 in areas of Asia to the north and east of the Caspian Sea. In high-incidence areas such as India, the Transkei (southern Africa), and the Gonbad region in northern Iran, the incidence in females approaches or exceeds that in males.^{67,68} More than 60% of the annual esophageal cancer deaths in the world are reported in China, where it is the second most common cancer after stomach cancer.

The highest age-adjusted incidence rates in the United States have been registered in African Americans, Hawaiians, and Alaskan Natives. Epidemiologic studies have implicated a variety of risk factors including tobacco, alcohol, low consumption of fresh fruits and vegetables, deficiencies of specific antioxidant micronutrients, and consumption of foods contaminated by mycotoxins or containing nitrosamine precursors.

Previously, at least 90% of esophageal cancers were classified as squamous cell carcinomas. During the past 20 years, particularly in US White males, the incidence of adenocarcinoma of the esophagus has increased more rapidly than the incidence of any other upper digestive or gastrointestinal cancer. Whereas the reported incidence of squamous cell carcinoma of the esophagus among US White and African American men and women was relatively stable during 1975 to 1995, the incidence

of adenocarcinoma of the esophagus increased by more than 100% among White men and by about 50% among White women. The African American-White age-adjusted incidence rate ratio or estimated relative risk was 5.6 for squamous cell carcinoma and 0.3 for adenocarcinoma of the esophagus.⁶⁹

Squamous cell carcinomas are located mainly in the middle third rather than in the distal third of the esophagus. Esophageal adenocarcinomas are generally located in the lower third of the esophagus, in association with Barrett intestinal metaplasia, a condition wherein the squamous epithelium of the distal esophagus is replaced by columnar epithelium and mucus-secreting goblet cells. The diagnosis is made by endoscopy and biopsy. The histogenesis of Barrett's columnar epithelial metaplasia is attributable to chronic inflammatory injury as a result of protracted gastroesophageal reflux. Normally, the lower esophageal sphincter, the crural diaphragm that encircles the esophagus as it enters the abdomen, and swallowing-induced peristalsis serve as protective barriers against the retrograde escape of gastric refluxate.⁷⁰

The reported incidence of adenocarcinoma in Barrett esophagus with dysplasia, 0.5% per year, is about 30 to 125 times that of the general population.^{71,72} Individuals with long-segment Barrett esophagus (3 cm or greater) experience higher risk than those with the more common short-segment lesion. The probable morphologic sequence of events consists of: chronic esophagitis, mucosal ulcerations accompanied by partial epithelial regeneration and repair, Barrett esophagus (metaplasia), high-grade dysplasia, and neoplasia (Figure 1). Biomarkers of neoplastic progression of Barrett mucosa include loss of heterozygosity at chromosomes 9p and 17p, aneuploidy, and polyploidy.⁷³ Nitrosamines, nitrosamides, and N-nitroso compounds are potent experimental carcinogens for the esophagus. The nitrosamines that affect the esophagus are metabolized in the target organ and result in the formation of genotoxic compounds that alkylate DNA at the O⁶ position of guanine. Human exposure to nitrosamines and nitrosamine precursors may emanate from in-

gested foods, drinking water, the volatile fraction of tobacco smoke, industrial air emissions, and medications.⁷⁴ Studies of lifestyle risk factors associated with adenocarcinoma of the esophagus have underscored current cigarette smoking, obesity, a history of hiatal hernia, and medications that relax or alter the gastroesophageal fibromuscular junctional structures.⁷⁵⁻⁷⁷

In sharp contrast to the trend of declining incidence of gastric cancer located in the antrum or corpus, investigators in various countries of North America and Europe have reported rising incidence rates for adenocarcinoma of the gastric cardia in parallel with increases in esophageal adenocarcinoma. In the United States, based on data from the Surveillance, Epidemiology, and End Results program, the incidence of gastric cardia adenocarcinoma among White males now equals the rate for gastric cancers in other anatomic locations. In Sweden, the incidence of gastric cardia carcinoma after 1970 exhibited an average annual increase of 2.5%. Interpretation of the magnitude of the increasing trends for gastric cardia cancer may be biased by the extent of misclassification of esophageal adenocarcinoma and noncardia stomach cancer. However, the temporal and racial patterns by pathologic cell type and anatomic location, and the commonality of risk factors associated with gastroesophageal reflux disease, would suggest that the classification of gastric cardia adenocarcinoma and esophageal adenocarcinoma may represent a single pathophysiologic and epidemiologic entity.^{61,78,79}

CHRONIC CHOLECYSTITIS AND CHOLELITHIASIS

Global age-standardized incidence rates for gallbladder cancer are higher in women than in men, and highest in countries in Eastern Europe, northern and eastern parts of India, Japan, Korea, and in South American populations with Indian admixture or ethnicity such as the Mapuche Indians in Chile. In these populations, there is significant concordance of surgical interventions for gallstones and gallbladder cancer incidence. The elevated risk of gallbladder cancer among American Indians, as in the Pima Indians in the southwestern United States, is positively correlated with the in-

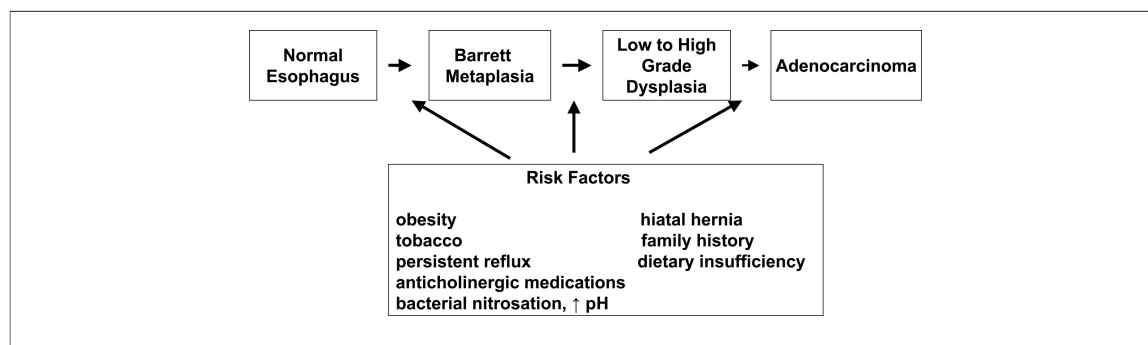


FIGURE 1 Epidemiology and Pathogenesis of Adenocarcinoma of the Esophagus and Gastric Cardia. Reprinted with permission from Schottenfeld and Beebe-Dimmer.¹⁰

creased prevalence of cholecystitis, cholelithiasis, and obesity.⁸⁰⁻⁸²

In the United States, cholelithiasis and chronic cholecystitis affect 25% of women and 10% to 15% of men over age 50, among whom 1 million new cases are diagnosed each year. Three principal defects contribute to gallstone formation: cholesterol supersaturation, accelerated cholesterol crystal formation, and gallbladder hypomotility. Stasis of bile within the gallbladder lumen incurs damage to the mucosa, resulting in the release of intracellular enzymes and activation of a cascade of inflammatory mediators (eg, prostaglandins, phospholipases). Gallbladder cancer arises usually as a consequence of chronic inflammation in association with gallstones; however, the cumulative risk of cancer after 20 years of follow up is about 1%, representing a threefold increase in risk compared with those without a history of cholecystitis. Risk factors for cholesterol-containing gallstones and cholecystitis such as obesity, hyperlipidemia, use of oral contraceptives or estrogen replacement therapy, and multiple pregnancies influence cholesterol hypersecretion and bile acid hyposecretion, gallbladder hypomotility and biliary stasis, or the release of inflammatory cytokines. The risk of gallbladder cancer increases with size and duration of gallstones and calcification in the mucosal epithelium ("porcelain gallbladder").⁸³ Genetic factors influencing cholesterol synthesis and metabolism, or the formation of "lithogenic bile," have been suspected based on racial patterns and familial history. An additional risk factor for gallbladder cancer is a congenital malformation described as anomalous junction of the pancreatic and common bile

ducts. It is more commonly associated with gallbladder cancer in Japan.⁸⁴⁻⁸⁸

CHRONIC INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) provides an additional example of increased risk of neoplasia experienced by patients with chronic inflammation in gastrointestinal tissues. Ulceroinflammatory disease in ulcerative colitis (UC) is confined to the mucosa and submucosa and may extend throughout the rectum and colon; in approximately 10% of patients, the distal ileum may be involved ("backwash ileitis"). Crohn disease (CD) is characterized by a transmural inflammatory process in the large or small intestine that exhibits mucosal damage, noncaseating granulomas, fissuring, and fistula formation. A classical feature of CD when multiple bowel segments are involved is the demonstration of "skip" lesions with intervening clinically normal bowel. The pathogenesis of IBD suggests that there has been an aberrant immune response to luminal indigenous microorganisms or ingested foreign antigens. The inflammatory response mediated by CD4+ T-cells is exaggerated, unregulated, and cytotoxic. The mucosal ulcerations would allow for microbial flora to gain access to submucosal lymphoid tissue and thus trigger an immune response.⁸⁹⁻⁹³

The risk of colorectal cancer in IBD patients increases with longer duration of disease and with extent of involvement of the large intestine. In addition, the risk increases with the appearance and higher grade of dysplastic lesions. Dysplastic areas may appear flat or pol-

ypoid, localized, multifocal, or diffuse. The multicentricity of neoplasms commonly seen in IBD reflects “field cancerization” and suggests intraepithelial spread of preinvasive neoplastic cells or multiple clones of tumors. After an induction-latency interval up to 10 to 15 years, the risk of cancer increases at the rate of 0.5% to 1% per year. Colitis-associated colorectal cancer is diagnosed at a younger age than sporadic colorectal cancer in the general population, and more often exhibits a mucinous or signet-ring cell histology. The molecular pathogenesis of colitis-associated colorectal cancer, as in sporadic colorectal cancer, is characterized by genomic instability, microsatellite instability, aneuploidy, allelic deletions as in *TP53*, and aberrant methylation of promoter sequences in mismatch repair genes. Unlike normal colonic mucosa, however, inflamed colonic mucosa demonstrates abnormalities in various molecular pathways before histologic evidence of dysplasia or cancer.^{94–96} IBD may be associated with manifestations of chronic inflammation and neoplasia in the biliary ductal system. An example of this is primary sclerosing cholangitis (PSC), which occurs in approximately 3% of patients with ulcerative colitis and less frequently (about 1%) in patients with Crohn disease.⁹⁷ PSC is characterized by inflammation, cholestasis, and fibrosis in the intrahepatic and extrahepatic biliary ducts. The frequency of cholangiocarcinoma in patients with PSC has been estimated to vary between 5% and 20%. Manifestations of UC may be evident in 70% of PSC patients. The clinical course in PSC is not affected by medical or surgical treatment of IBD, suggesting common susceptibility and pathogenic factors rather than that IBD is a direct cause of PSC.

INFLAMMATORY ATROPHY AND PROSTATE CANCER

A suggestive association of prostatic inflammation and carcinogenesis has been described, but investigators have not identified a causal agent. Namely, a pathologic entity of chronic inflammation associated with focal hyperplasia and inflammatory atrophy has been reported. Such

lesions occur most frequently in the peripheral zone of the prostate, wherein most lesions (> 70%) of intraepithelial neoplasia and invasive adenocarcinoma are observed. Merging or morphologic transition of proliferative inflammatory atrophy, intraepithelial neoplasia, and invasive adenocarcinoma have been reported by some but not all pathologists.^{98–103}

The focal areas of inflammation presumably develop in response to oxidative stress. The cyclo-oxygenase (COX) 2 enzyme is overexpressed in the macrophages and epithelial cells in lesions of proliferative inflammatory atrophy. COX-2 is the inducible isoform of COX that converts an array of fatty acid substrates into proinflammatory prostanoids (eg, prostaglandin E₂). Multiple examples of solid tumors, such as in the colon, esophagus, pancreas, lung, urinary bladder, breast, and uterine cervix, have demonstrated overexpression of COX-2 and of the glutathione S-transferase isoenzymes that act as “scavengers” of reactive oxygen species.¹⁰⁴ Of additional interest are the preliminary reports of preclinical and clinical studies of potential chemopreventive benefits and of measured risks of regular use of anti-inflammatory agents in prostate cancer and superficial bladder cancer, and the more compelling evidence from randomized clinical trials in preventing recurrent adenomatous polyps.^{105,106}

OBSTRUCTIVE AIRWAY DISEASE

In the early 1960s, Passey hypothesized that it was the irritating properties of tobacco smoke, resulting in chronic bronchitis and inflammatory destruction of lung tissue, which were of pathogenic significance in the causal pathway of lung cancer, rather than any direct action by volatile and particulate carcinogens in tobacco smoke.¹⁰⁷ The experiments of Kuschner, however, suggested that bronchial and bronchiolar inflammation, accompanied by reactive proliferation, squamous metaplasia, and dysplasia in basal epithelial cells, provided a co-carcinogenic mechanism for neoplastic cell transformation on exposure to polycyclic aromatic hydrocarbons.¹⁰⁸ Continued smoking in association with chronic obstructive pulmonary disease (COPD), when

accompanied by moderate or marked cytological atypia in exfoliated cells in the sputum, was significantly predictive of lung cancer in the Colorado Cancer Center Sputum Screening Cohort Study.¹⁰⁹

Although cigarette smoking is the predominant cause of COPD, with an estimated attributable (etiologic) risk fraction exceeding 80% in smoking affected individuals, perhaps only 10% to 15% of current smokers will eventually develop clinically significant sequelae of productive cough, exertional dyspnea, and cardiovascular disease.¹¹⁰ There are at least 10 cohort studies indicating that chronic obstructive airway disease is an independent predictor of lung cancer risk, and various studies reported an increased risk of lung cancer among adults with asthma, tuberculosis, or postinflammatory pulmonary interstitial fibrosis, such as in patients with silicosis and asbestosis.¹¹¹⁻¹¹⁸

Chronic cigarette smoking retards mucociliary clearance of foreign particulates and respiratory tract secretions, evokes an inflammatory response accompanied by fibrosis and thickening in the membranous and respiratory bronchioles, and causes mucus gland hypertrophy, hyperplasia, and dysplasia in the proximal airways.¹¹⁹ The manifestations of COPD signal the extent of bronchopulmonary structural and functional damage arising from the interaction of sustained exposure to toxic products of tobacco combustion and host susceptibility. In this context, COPD is a biomarker of cumulative exposure dose level and tissue susceptibility. Ito, et al.¹²⁰ reported that the severity of chronic obstructive respiratory symptoms and impaired pulmonary function was correlated with a reduction in histone deacetylase activity (HDAC) in lung tissue and alveolar macrophages. A key enzymatic function of HDAC is the inhibition or modulation of production of proinflammatory cytokines and matrix metallo-

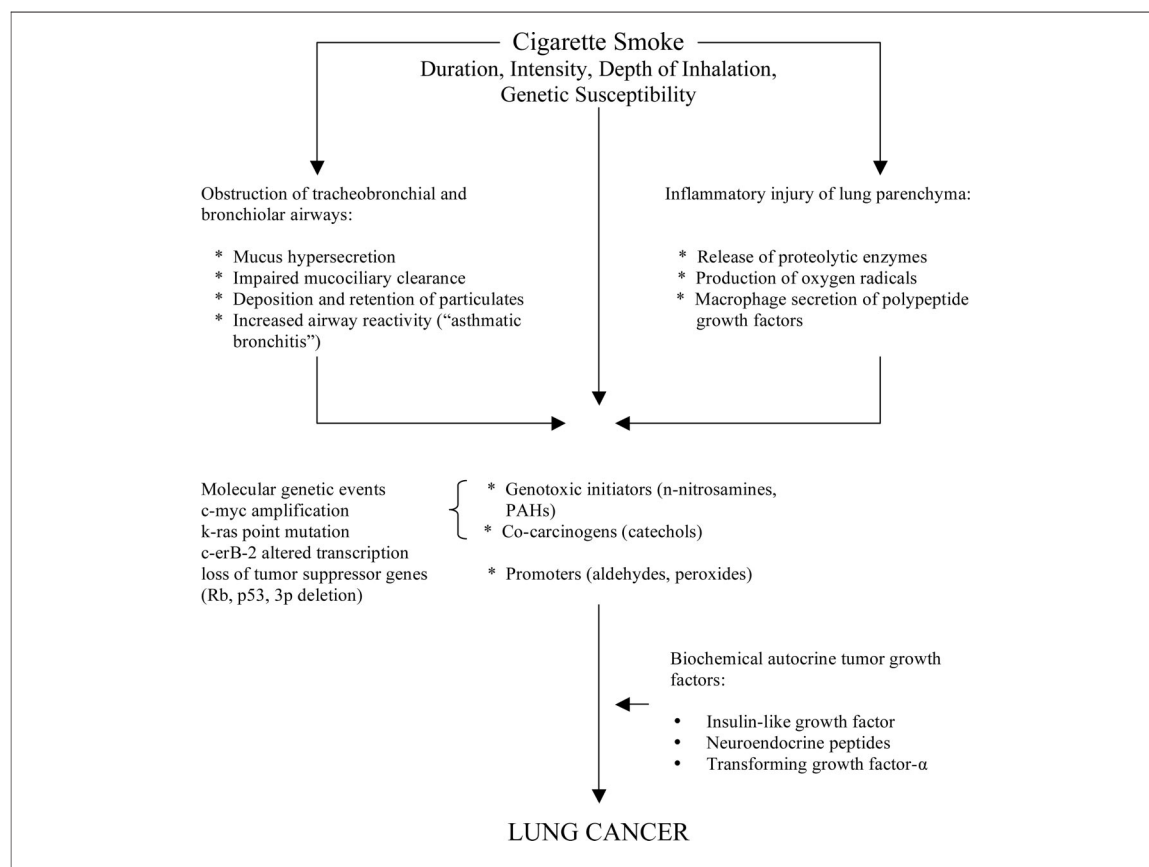


Figure 2 Enhancement of the Causal Pathway of Cigarette Smoke and Lung Cancer by the Association of Chronic Obstructive Pulmonary Disease. Reprinted with permission from Islam and Schottenfeld.¹¹³

proteinases (MMPs) by macrophages. MMPs are a family of secreted zinc metalloproteases that degrade collagens in the extracellular matrix and thereby facilitate tumor progression. A conceptual model may be structured that incorporates the tumorigenic effects of chronic obstructive inflammatory disease in the causal pathway of cigarette smoke and lung cancer (Figure 2). The molecular events in the natural history of lung cancer comprise multiple genetic mutations that are determinants of neoplastic transformation and tumor progression, and the elaboration of autocrine growth factors that influence the clonal behavior and morphologic features of neoplastic cells.^{121–124} Chronic inflammation in the proximal and distal bronchial airways is an important cause of obstructive symptoms and provides the dynamic setting for oxidative stress and the formation of free radicals that accompany the reparative proliferative response.¹²⁵ Increased proliferation kinetics and the interaction of hydroxyl radicals with DNA augment the likelihood of DNA structural and transcriptional errors.

Chronic interstitial infiltrative lung disease encompasses a variety of disorders including the category of occupational and environmental pneumoconioses (eg, silicosis, asbestosis). Chronic diffuse interstitial diseases of the lung generally begin as alveolitis and bronchiolitis. A critical event in pathogenesis is the recruitment and activation of inflammatory leukocytes and alveolar macrophages. Interactions among inflammatory cells and the release of cytokines stimulate progressive pulmonary fibrosis.¹²⁶

Silicosis of the lung is caused by inhalation of crystalline silicon dioxide. As with other pneumoconioses, the risk increases with the concentration level and duration of exposure. Persons with silicosis are at increased risk for mycobacterial infection. Although still controversial, the International Agency for Research on Cancer has classified inhaled crystalline silica (eg, quartz, cristobalite) as a human carcinogen.¹²⁷ Asbestos, a family of crystalline hydrated silicates, when in-

haled over a protracted interval of time, may be associated with pulmonary fibrosis (asbestosis), carcinoma of the lung or larynx, and pleural or peritoneal malignant mesothelioma.^{128,129}

EPILOGUE

Recurrent or persistent inflammation, whether due to exposure to a specific infectious or chemical agent, radiation or physical trauma, or as a result of aberrant immune response mechanisms, may induce, promote, or influence susceptibility to carcinogenesis by causing DNA damage, inciting tissue reparative proliferation, and/or by creating a stromal “soil” that is enriched with cytokines and growth factors. This review would suggest that clinically and pathologically classifiable inflammatory diseases are established precursors of cancers occurring in gastrointestinal, respiratory, anogenital, and lymphoid organs and tissues. However, an assessment of the pathophysiologic and molecular dynamics of chronic inflammation and carcinogenic mechanisms suggests areas of intersection that are mutually instructive in a larger context.

The illuminating view of tumors as “wounds that do not heal” focuses on the formation and composition of tumor stroma and neoplastic cell-stromal cell interactions. Stromal content is comprised of a fibrin-gel matrix, connective tissue elements, and a variable component of infiltrating inflammatory cells, which create a signaling microenvironment of proinflammatory agents such as the COX-2 enzyme and prostaglandins, chemokines, and interleukins in which transformed cells prosper. Future research on the complex cascade of cellular and humoral factors participating in the chronic inflammatory response will further understanding of the pathogenesis of the common degenerative diseases and potentially provide a rationale for targeted cancer chemopreventive interventions.

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