Table 7-4 Chronic Inflammatory States and Cancer

Pathologic Condition	Associated Neoplasm(s)	Etiologic Agent
Asbestosis, silicosis	Mesothelioma, lung carcinoma	Asbestos fibers, silica particles
Inflammatory bowel disease	Colorectal carcinoma	
Lichen sclerosis	Vulvar squamous cell carcinoma	
Pancreatitis	Pancreatic carcinoma	Alcoholism, germline mutations (e.g., in the trypsinogen gene)
Chronic cholecystitis	Gallbladder cancer	Bile acids, bacteria, gallbladder stones
Reflux esophagitis, Barrett esophagus	Esophageal carcinoma	Gastric acid
Sjögren syndrome, Hashimoto thyroiditis	MALT lymphoma	
Opisthorchis, cholangitis	Cholangiocarcinoma, colon carcinoma	Liver flukes (*Opisthorchis viverrini*)
Gastritis/ulcers	Gastric adenocarcinoma, MALT lymphoma	*Helicobacter pylori*
Hepatitis	Hepatocellular carcinoma	Hepatitis B and/or C virus
Osteomyelitis	Carcinoma in draining sinuses	Bacterial infection
Chronic cervicitis	Cervical carcinoma	Human papillomavirus
Chronic cystitis	Bladder carcinoma	Schistosomiasis

Adapted from Tlsty TD, Coussens LM: Tumor stroma and regulation of cancer development. Ann Rev Pathol Mech Dis 2006;1:119.

Precursor lesions can be defined as localized morphologic changes that are associated with a high risk of cancer. Virtually all precursor lesions arise in epithelial surfaces and are associated with an increased risk of various forms of carcinoma.

- ***Chronic inflammation and cancer.*** A cause-and-effect relationship between chronic inflammation and cancer was first proposed by Virchow in 1863, and it is now appreciated that cancer risk is increased in individuals affected by a variety of chronic inflammatory diseases, including those with infectious and noninfectious etiologies (Table 7-4). As with any cause of tissue injury, each of these disorders is accompanied by a compensatory proliferation of cells that serves to repair the damage. In some cases, chronic inflammation may increase the pool of tissue stem cells, which may be particularly susceptible to transformation. Additionally the activated immune cells produce reactive oxygen species that are directly genotoxic. as well as inflammatory mediators that may promote bystander cell survival, even in the face of genomic damage. Chronic epithelial injury often leads to metaplasia, the replacement of one cell type with a second that is better able to survive the ongoing insult. In the short term, these changes can be adaptive; the organism must survive, and the damaged cells can be repaired or eliminated later. However, over longer time periods (years to decades) such alterations may allow cells with potentially oncogenic mutations to survive, eventually leading to cancer. Whatever the precise mechanism, the link between chronic inflammation and cancer has practical implications. For instance, diagnosis and effective treatment of *Helicobacter pylori* gastritis with antibiotics can quell a chronic inflammatory condition that might otherwise lead to the development of a gastric cancer.
- ***Precursor lesions and cancer.*** As mentioned, the term *precursor lesion* encompasses several entities that are associated with increased cancer risk. Precursor lesions do not inevitably progress to cancer; nevertheless, they are important to recognize because some precursor lesions can be detected by screening procedures and treated, thereby reducing the risk of developing cancer.

  Many precursor lesions arise in the setting of chronic inflammation and can be recognized by the presence of metaplasia: examples include *Barrett esophagus* (gastric and colonic metaplasia of the esophageal mucosa in the setting of gastric reflux); *squamous metaplasia* of the bronchial mucosa (in response to smoking) and the bladder mucosa (in response to schistosomiasis infection); and *colonic metaplasia* of the stomach (in the setting of pernicious anemia and chronic atrophic gastritis). Other precursor lesions are noninflammatory hyperplasias. One of the most common precursor lesions of this type is *endometrial hyperplasia*, which is caused by sustained estrogenic stimulation of the endometrium. Another relatively frequent precursor lesion is *leukoplakia*, a thickening of squamous epithelium that may occur in the oral cavity or on the penis or vulva and give rise to squamous carcinoma.

  The final group of precursor lesions is benign neoplasms that are at risk for malignant transformation. The classic example of a neoplastic precursor lesion is the colonic *villous adenoma*, which if left untreated progresses to cancer in about 50% of cases. It should be emphasized, however, that most benign tumors transform rarely (e.g., uterine leiomyomas, pleomorphic adenoma) and others not at all (e.g., lipomas). Why many benign tumors have a negligible risk of malignant transformation is an unsettled question; one possibility is that benign tumors at high risk for malignant transformation possess the cancer-enabling property of genomic instability (discussed later), whereas truly benign tumors do not.
- ***Immunodeficiency states and cancer.*** Patients who are immunodeficient, and particularly those who have deficits in T-cell immunity, are at increased risk for cancers, especially those caused by oncogenic viruses. These virally associated tumors include mainly lymphomas, but also certain carcinomas and even some sarcomas and sarcoma-like proliferations. The complex relationship between infections, immunity, and cancer are discussed later in this chapter.

Genetic Predisposition and Interactions Between Environmental and Inherited Factors

In some families cancer is an inherited trait, usually due to germline mutations in a tumor suppressor gene (described