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Original article

The cancer burden attributable to biologic agents

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ABSTRACT

Purpose: A review of cohort and case-control studies that attempt to quantify the proportion of cancer cases diagnosed in the United States and throughout the world that may be attributed to biologic or infectious agents.
Methods: Epidemiologic studies published primarily since the year 2000 are summarized that estimate population attributable fractions based on consensus estimates of relative risk and of the exposure prevalence to putative oncogenic infectious agents in representative populations.
Results: The proportion of incident cancers attributable to infectious agents diagnosed in low- and middle-income countries, comprising more than 80% of the world's population, has been estimated to vary from 20% to 30%, in contrast to a range of 5% or less to 10% in the United States and other highly industrialized populations. More than 90% of the global cancer cases attributed to infectious agents have been caused by hepatitis B virus, hepatitis C virus, human papillomaviruses, and the gram-negative bacterium, *Helicobacter pylori*.
Conclusions: Epidemiologic and pathologic studies that use molecular diagnostic probes and immunologic and biochemical assays have described the substantial impact of infectious agents on global cancer incidence. These compelling observations have stimulated the development of effective hepatitis B virus and human papillomavirus vaccines and the rationale for eradication of *Helicobacter pylori*.

The proportion of incident cancers diagnosed in low- and middle-income countries attributable to infectious agents was estimated to vary between 20% and 30%, in contrast to that of 5% or less to 10% estimated in the United States and other highly industrialized countries [1]. Of the 12.7 million new cancer cases that were diagnosed worldwide in 2008, about two million were attributable to infectious agents (15.7%), of which 1.6 million were diagnosed in low- and middle-income countries composing more than 80% of the world's population [2]. Infections caused by hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomaviruses (HPVs), and the gram negative bacterium *Helicobacter pylori* accounted for more than 90% of global cancer cases attributable to infectious agents. In a summary of the global burden of cancers attributable to infectious agents in 2008, de Martel et al. described 600,000 cancers of the liver associated with HBV and HCV (29.5%), 610,000 HPV-related cancers (30.0%), and 660,000 gastric cancers associated with *H. pylori* (32.5%) [3]. Seven viruses, including Epstein–Barr, HBV, HCV, Kaposi sarcoma herpes virus, human immunodeficiency virus type-1 (HIV-1), HPV, and human T-cell lymphotrophic virus type-1, have been classified as group 1 human carcinogens by the International Agency for Research on Cancer (Table 1).

In population-based studies to be reviewed, efforts to quantify the proportion of cancer cases attributable to infectious agents used some variant of the population attributable fraction (PAF). As a valid measure of the population burden of disease associated with a specific risk factor, it was assumed that the estimate was not influenced by selection or misclassification bias, nor confounded by the uncontrolled distribution of covariate causal factors [4–6]. In recent publications, inferences about the magnitude and precision of relative risk associated with a specific biologic agent and cancer site were based on the International Agency for Research on Cancer Monograph on the Evaluation of Carcinogenic Risks to Humans [7]. The formula for deriving the PAF proposed by Morton Levin in 1953 is for a single binary exposure variable: $\%PAF = [pe\ (RR - 1)/pe\ (RR - 1) + 1] \times 100$, where pe is the proportion of a sample of the study or target population exposed, and RR is the risk ratio, rate ratio, or odds ratio (OR) [8].

When the exposure is classified into more than two categories or levels, the formula is modified to indicate summation of the products of the proportion of the study population in each exposure

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Table 1
Biologic agents and human cancers

Agent	Organ site (s)
Viruses	
HPV	uterine cervix; oropharyngeal; anogenital
HBV/HCV	Liver, non-Hodgkin lymphoma (HCV)
EBV	Lymphoid tissues: non-Hodgkin lymphomas, including Burkitt, AIDS-related, posttransplant lymphoproliferative disorders; Hodgkin lymphoma; Epithelial tissues: nasopharyngeal carcinoma, gastric carcinoma (?)
HHV-8	Kaposi sarcoma; primary effusion lymphoma; Castleman multicentric lymphoproliferative disease
HTLV-1	T-cell leukemia; lymphoma
MCPyV	Merkel cell carcinoma (neuroendocrine tumor of dermis)
Bacteria	
Helicobacter pylori	Stomach: carcinoma, B-cell MALT lymphoma
Parasites	
Schistosoma haematobium	Urinary bladder
Liver flukes	Liver; bile duct; cholangiocarcinoma
Fungi	
Aspergillus (aflatoxin)	Liver

EBV = Epstein–Barr virus; HHV-8 = human herpes virus 8; HTLV-1 = human T lymphotropic virus-1; MALT = mucosa-associated lymphoid tumor; MCPyV = Merkel cell polyoma virus. Reprinted with permission of the Annual Review of Public Health [1].

level (pi) and the stratum-specific estimations of relative risk: $\%PAF = [\sum pi \times (RRi - 1)/1 + \sum pi \times (RRi - 1)] \times 100$.

In several of the studies to be reviewed, the derivation of PAF was based on the proportion of cases exposed, rather than the prevalence of the infectious agent in the population, multiplied by the attributable fraction among the exposed cases (AFe), where $AFe = RR - 1/RR$.

The tumorigenic effects of persistent infections by viral, bacterial, and parasitic agents are mediated through mechanisms of chronic inflammation that sustain proliferative signaling and evoke aberrant adaptive immune responses. In the absence of a prominent inflammatory response, integration of segments of the microbial genome within the host genome may be accompanied by disruption of tumor-suppressing regulatory mechanisms [9,10].

Hepatitis B and C viruses

The GLOBOCAN 2008 data base reported that the incidence of primary liver cancer, predominantly hepatocellular carcinoma (HCC), ranked fifth in men (superseded by lung and bronchus, prostate, colon and rectum, and stomach cancers) and made up about 8% of global cancer incidence in men, and seventh in women (superseded by breast, lung, and bronchus, colon and rectum, stomach, cervix uteri, and corpus uteri cancers) or about 4% of global cancer incidence in women [11].

Hepatitis B virus

The incidence of HCC is highly correlated with the prevalence of chronic HBV infection. The highest prevalence proportions of chronic HBV infection, as determined by the persistence of hepatitis B surface antigen (HBsAg) in serum, at levels of 8% or more in the population, are reported in Eastern Asia and sub-Saharan Africa. These two geographic areas compose 85% of global incident HCC. High-risk countries such as Taiwan, Laos, Vietnam, China, and South Korea have registered age-standardized rates of HCC between 20 and 35 per 100,000 [12,13]. Chronic HBV infection levels between 2% and 7% are observed in Northern Africa, Western and Southern Asia, and Eastern Europe. Levels at less than 2% are reported in North America, Western Europe, and Australia. HCC rates per 100,000 in areas of the United States and Canada vary between 3.3 and 4.5. In the United States, HCC rates are highest among Asian Americans and Pacific Islanders. Variability by race and ethnicity is evident when comparing US whites (3.9) with US blacks (7.0), Hispanics (8.0), and Native Americans/Alaska Natives (6.6) [14,15].

HBV infection generally results after percutaneous and mucosal exposures to contaminated blood, semen, vaginal secretion, other body fluids, and injected materials. In countries where HBV infection is highly endemic, common modes of transmission include perinatal transmission from the HBsAg+ mother to infant, in particular, the mother who also exhibits HBe antigen positivity, and horizontally from child-to-child transmission in household, day care, and school settings [16–18]. In acute hepatitis B, HBsAg appears in the serum 2 to 10 weeks after exposure to the virus and may serve as a marker of past exposure; the presence of HBeAg in patients with chronic hepatitis generally indicates a high level of viral replication and thus infectivity. The age when infection occurs is an important factor in determining risk of chronic infection. Approximately 80% to 90% of infected infants develop a chronic infection, in contrast to 2% to 5% of adults [19].

The natural history of chronic HBV infection may be described in four phases: immune tolerant, immune clearance, nonreplicating, or most problematic, reactivation, and progressive degeneration. The different phases are dynamic and potentially reversible, depending on host immune responses and the duration and severity of liver injury. Immune responses to infected hepatocytes trigger a procarcinogenic inflammatory cascade associated with a recurring cycle of necrosis and regeneration fostering the accumulation of genetic and epigenetic pathogenic effects. A majority of patients with low-risk immunologic markers, namely patients who are negative for HBeAg and positive for antibodies to HBeAg exhibit low incidence of cirrhosis and HCC [20–22]. The risk of HCC in persons with HBV-related cirrhosis is estimated between 2 and 4 per 100 person-years, compared with less than 1 per 100 person-years in HBV-infected persons without cirrhosis [23]. In the pathogenesis of cirrhosis and HCC, other interactive causes of chronic liver injury have been attributed to concurrent HCV infection, HIV infection, excessive alcohol consumption, or exposure to high levels of aflatoxins produced by *Aspergillus flavus* and ingested in contaminated maize or peanuts or to exposure from cigarette tobacco [24–26]. These environmental agents may increase estimates of relative risks and confound estimates of PAFs for the independent burden of chronic HBV infection.

Hepatitis C virus

The estimated global prevalence of HCV infection is about 185 million cases. More than 350,000 deaths per year worldwide are attributable to HCV infection. .PAFs for HCC secondary to HCV have varied from 75% to 90% of cases in Japan, 60% to 75% of cases in Spain, and 31% to 47% of cases in the United States. The current prevalence of chronic HCV infection in the United States is estimated at 3 million children and adults. HCV, a ribonucleic acid virus in the Flaviviridae family, is primarily acquired as a result of percutaneous exposures to contaminated needles and syringes, rather than from infected mothers to their infants. Contaminated transfusions of blood products were an important route of transmission before HCV testing was introduced in the early 1990s. Persistence of HCV infection occurs in approximately 80% of acutely ill patients in whom 15% to 25% will develop cirrhosis [27,28]. Factors that accelerate progression to HCC include coinfection with HBV or HIV-1, and heavy alcohol consumption. Relative risks for the association between HCV seropositivity and HCC observed in eight