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 [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 [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 [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 [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 [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 [1].
Biologic agents and human cancers

<table>
<thead>
<tr>
<th>Agent</th>
<th>Organ site(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viruses</td>
<td></td>
</tr>
<tr>
<td>HPV</td>
<td>uterine cervix; oropharyngeal; anogenital</td>
</tr>
<tr>
<td>HBV/HCV</td>
<td>Liver, non-Hodgkin lymphoma (HCV)</td>
</tr>
<tr>
<td>EBV</td>
<td>lymphoid tissues: non-Hodgkin lymphomas, including Burkitt, AIDS-related</td>
</tr>
<tr>
<td></td>
<td>postransplant lymphoproliferative disorders; Hodgkin lymphoma;</td>
</tr>
<tr>
<td></td>
<td>epithelial tissues: nasopharyngeal carcinoma, gastric carcinoma (?)</td>
</tr>
<tr>
<td>HHV-8</td>
<td>Castleman multicentric lymphoproliferative disease</td>
</tr>
<tr>
<td>HTLV-1</td>
<td>T-cell leukemia; lymphoma</td>
</tr>
<tr>
<td>MCPyV</td>
<td>Merkel cell carcinoma (neuroendocrine tumor of dermis)</td>
</tr>
<tr>
<td>Bacteria</td>
<td></td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>Stomach: carcinoma, B-cell MALT lymphoma</td>
</tr>
<tr>
<td>Schistosoma haematobium</td>
<td>Urinary bladder</td>
</tr>
<tr>
<td>Liver flukes</td>
<td>Liver; bile duct; cholangiocarcinoma</td>
</tr>
<tr>
<td>Fungi</td>
<td>Aspergillus (aflatoxin)</td>
</tr>
</tbody>
</table>

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: 

\[ \%PAF = \left( \sum \pi_i \times (RR_{i} - 1) / 1 + \sum \pi_i \times (RR_{i} - 1) \right) \times 100. \]

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 (Af), 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
cohort studies have ranged from 2.5 to 88 [29,30]. The wide range in the reported relative risks most likely reflected variations in the cohort prevalence of HCV and duration and severity of liver disease or the failure to control adequately for confounding by coinfections with HBV or HIV.

Primary prevention of HCC

In 1992, the World Health Organization established the goal of universal HBV immunization. By 2009, 92% of the 193 member countries had developed HBV immunization programs for infants and children. Globaly, 70% of infants had received three doses of the recombinant vaccine [31]. Based on the studies conducted in several high-risk countries, the immunization programs were projected to reduce the prevalence of chronic HBV infection from between 8% and 20% to less than 2%, with consequent reduction of approximately 50% in HCC incidence in children and adults [32]. This would impact future estimates of attributable risks of cirrhosis and HCC because of persistent HBV infection. Currently, a global program of active or passive immunization against HBV is not available. However, the treatment of HCV is evolving rapidly with the introduction of direct-acting antiviral agents, such as protease or nucleotide polymerase inhibitors that interfere with the viral replication cycle. One or more of these agents may be administered concurrently with drugs that target host immune responses (e.g., pegylated interferon alfa) [28,30].

H. pylori and gastric cancer

H. pylori is a gram-negative multilagellated bacterium that colonizes primarily on the luminal mucosal surface of the pyloric antrum and body (corpus) of the stomach. Chronic H. pylori infection is an established causal agent of gastric (body), pyloric and duodenal ulcers, multifocal atrophic gastritis, noncardia gastric adenocarcinoma and gastric mucosal-associated B-cell lymphoid-tissue (MALT) lymphoma [10]. H. pylori exhibit unique morphologic, genetic, metabolic, and immunologic features that enable it to thrive in an extremely acidic (pH, 1.5–3.5) and proteolytic environment. The organism is typically spiral shaped with 2 to 6 unipolar sheathed flagella which allow for enhanced motility through the viscous mucosal layer over gastric epithelial cells [10,33]. H. pylori strains appear to be genetically heterogeneous and adaptable to a changing environment. These characteristics may at least partially explain its ability to evade host-mediated immune responses and to acquire resistance to antimicrobial therapeutic agents [33,34]. Numerous (23) species of H. pylori have been identified, characterized by the expression of antibodies against different immunologic proteins that are associated with pathogenic virulence, such as the cytotoxin-associated antigen and vacuolating cytoxin A. Strains possessing these cytotoxins are associated with increased inflammation and mucosal damage.

H. pylori persist mainly in the surface mucus layer, adhering to the receptor for blood group antigen A. H. pylori adapt to stomach acidity by producing large amounts of the enzyme urease. Urease catalyzes hydrolysis of urea in the gastric juice to yield alkaline ammonia and carbon dioxide, resulting in the production of bicarbonate and the neutralization of acidity that facilitates survival of the bacteria [10,35]. H. pylori infection can be detected on endoscopic biopsy of the gastric mucosa and by means of non-endoscopic testing for IgG antibodies to H. pylori in serum or for H. pylori–specific antigens in a stool sample. The urea breath test involves drinking carbon-labeled urea that is converted to labeled carbon dioxide by the urease produced by H. pylori. The labeled gas is measured in a breath sample and has a sensitivity and specificity of 95%. This test has utility in assessing whether the organism has been eradicated after treatment [35].

At least 50% of the world’s population is infected with H. pylori [36]. There is significant geographic variation in the prevalence of infection, ranging from 20% or less in highly industrialized countries to as high as 80% to 90% in developing countries [37]. In high-risk countries, the initiation of infection occurs by 10 years of age and persists throughout life unless specifically treated. Infection rates are highest in Asia and Latin America, particularly in densely populated areas with poor hygiene and nutrition. Intrafamilial clustering of infection suggests oral–oral and fecal–oral routes of transmission. Using data from the National Health and Nutrition Examination Survey, it is estimated that one-third of the US adult population is infected, with significantly higher seroprevalence among Hispanics and African Americans compared with non-Hispanic whites. Older age, male gender, lower socioeconomic status, and birth outside the United States have been shown to be independently associated with increased H. pylori seropositivity [38].

Gastric cancer is the fourth most common cancer diagnosed with an estimated 989,000 new cases worldwide. It is also the second most common cause of cancer mortality with nearly 740,000 deaths annually [11]. In the United States, gastric cancer is a much less common cause of cancer death than in Eastern Asia, Eastern Europe, and South America. The Surveillance Epidemiology and End Results data for 2005 to 2009, reported age-standardized mortality rates of 4.3/100,000 in white men and 2.2/100,000 in white women [39]. Both gastric cancer incidence and mortality have declined worldwide over the past several decades, but most notably in industrialized countries [40–43].

In 1994, the International Agency for Research on Cancer recognized H. pylori as a group 1 carcinogen primarily for the established relationship with gastric cancer [7]. A meta-analysis of 14 case-control and five cohort studies reported an approximate twofold increase in risk (OR = 1.92; 95% confidence interval [CI] = 1.32–2.78). A subset analysis of studies with data available on location of tumor indicated H. pylori seropositivity was associated with an elevated risk of noncardia gastric adenocarcinoma (OR = 3.08; 95% CI = 1.78–5.31), but not of adenocarcinoma of the gastric cardia distal to the gastroesophageal junction (OR = 1.23; 95% CI = 0.56–2.71) [44]. Variability in risk estimates have been attributed to case-control or cohort study designs, tumor location, cell type (e.g., intestinal, diffuse, or mixed patterns) or socio-demographic characteristics of the population. The estimated prevalence or density of H. pylori infection tends to diminish as intestinal metaplasia and atrophic gastritis evolve, thus obscuring an accurate assessment, particularly in case-control studies, of the relative risk of the causative agent in the natural history of stomach cancer. It has been estimated that 60% to 90% of noncardia gastric cancer incidence may be attributable to H. pylori infection [2,3]. However, the fact that only a small percentage of chronically infected individuals, namely less than 1% to 3%, develop noncardia gastric adenocarcinoma underscores the importance of the indigenous virulence characteristics of the pathogenic agent in conjunction with other environmental and host co-factors in pathogenesis, including dietary patterns, exposure to tobacco, the availability and efficacy of antibiotic therapy, and the complex of genetic susceptibility and immune response determinants.

Human papillomaviruses

HPVs infect primarily stratified epithelia at cutaneous or mucosal sites. HPVs initiate anogenital infections in the germinal layer of dividing basal cells after penetrating microabrasions in the surface epithelium [45,46]. More than 100 types of HPVs have been
HPV 16 is carcinogenic for more than 50% of cases of cervical cancer. HPV 18 is the second most prominent cervical carcinogenic infection. HPV 16 and 18 are the most common types associated with cervical cancer among women aged 21 to 39 years, and are consistent with vaccine impact on reducing HPV-related disease [55]. The dynamic effect of enhanced utilization of the vaccine in young women and men will alter future estimates of attributable risk and attributable cases of HPV-related cancers.

References


