Infectious Causes of Malignancy and Their Potential Prevention

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Abstract There are numerous infectious etiologies of malignancy, both as direct causation or co-factors, as well as infections causing reduced immunity, allowing malignancies to express. Many of these infections are a major source of morbidity and mortality as well as a huge economic burden in large areas of the world. These malignancies include cervix, oral/anal, liver, gastric, nasopharyngeal, bladder carcinomas, and certain lymphomas, caused by a variety of viral, bacterial, and parasitic agents. For most of these agents, effective methods of prevention, barrier and/or immunization, and/or treatment have been developed. Socioeconomic factors show that the most preventable cancers caused by infections are highest in developing countries, raising important public health and priority issues.

Keywords bacteria; viruses; parasites; oncogenesis; cancer; prevention

1. Introduction

While for the first time in known human history, chronic non-infectious diseases have exceeded infections as the greatest cause of worldwide death [39], there is growing evidence to the existence of “hybrid” causes of malignancy whereby infections appear to play a major role [44]. Some have estimated that infections are second only to tobacco as the most common cause of cancer [60]. Many of these infection-induced malignancies occur in the developing world, are major economic and public health concerns, and are amenable to effective preventive measures.

2. The scope of the problem

2.1. Infectious causes of malignancy

It is estimated that 18% of the global cancers are attributable to infectious agents [3]. This is likely a low estimate as it includes only the known few oncogenic infectious agents and not many other suspected, but unproven, infectious causes. Also not included are conditions of chronic inflammation due to infections of any source, such as chronic osteomyelitis, sinus tracts, skin ulcers, and ultimately causing squamous cell carcinoma [24].

Several infectious agents including bacteria, viruses, and parasites have been implicated in oncology development (Table 1). Some of these are endemic in certain regions, such as hepatitis B virus (HBV) causing cirrhosis and hepatic carcinomas [21,29] and Epstein-Barr virus (EBV) associated with naso-pharyngeal carcinoma (NPC) and certain lymphomas [14,19]. Hepatic carcinoma and NPC are particularly prevalent in Southeast Asia and certain areas of the Pacific Islands and Africa, where transmission occurs vertically as well as horizontally, at least for HBV [47]. The transmission of EBV and, consequently, NPC is poorly understood but it certainly occurs in specifically defined geographic locales [56].

The association of human papillomavirus (HPV) with cervical cancer has been known for some time [13], but also recently an alarming increase in oral and anal carcinomas associated with this agent has been identified [25]. Moreover, while the overall incidence of worldwide cancer appears to be somewhat decreasing recently, it is rising for HPV-associated carcinomas. It has recently been proposed that the majority of head and neck carcinomas may be associated with HPV [15].

The human immunodeficiency virus (HIV) causing acquired immunodeficiency disease syndrome (AIDS) has been associated with high-grade lymphomas [57] and is a poor prognostic feature in this and most other associated malignancies unless AIDS is brought under control with a rise in the lymphocyte CD4 count. Kaposi’s sarcoma (KS) is frequently seen in AIDS, is associated with herpesvirus-8, and in East Africa is the most common malignancy associated with AIDS [17,23,30].

While many of the cancers caused by oncologic agents are distributed worldwide, there is a great disproportion with some having a much greater incidence in the developing world (Table 2). Thus, HBV infection (and hepatic carcinoma) is prevalent in Southeast Asia and Western Africa, but rather low in Eastern Europe and India [30]. Cervical cancer is much higher in regions where health care is limited and routine examinations uncommon. It has been...
Table 1: Known oncogenic agents.

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Viruses</th>
<th>Parasites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helicobacter pylori</td>
<td>Human papillomavirus—cervical, anal, vaginal, and oral carcinoma</td>
<td>Schistosomes—bladder carcinoma</td>
</tr>
<tr>
<td>gastric carcinoma, gastric lymphoma</td>
<td>Hepatitis B virus—liver</td>
<td>Opisthorchiasis, Clonorchis—cholangiocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Hepatitis C virus—liver</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Human immunodeficiency virus—lymphoma, Kaposi’s sarcoma, and facilitates all malignancies</td>
<td></td>
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<tr>
<td></td>
<td>Herpesvirus-8—Kaposi’s sarcoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epstein-Barr virus—Burkitt lymphoma, nasopharyngeal carcinoma, and possibly Hodgkin and other non-Hodgkin’s lymphoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Human T-lymphotropic virus 1—adult T-cell lymphoma and acute T leukemia and leiomyosarcoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>in immunodeficiency including AIDS</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Estimated cases of cancer caused by known infectious agents and percent in developing countries in 2008.

<table>
<thead>
<tr>
<th>Stomach cancer and lymphoma</th>
<th>990,000 cases (90% in developing countries)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer</td>
<td>530,000 cases (86% in developing countries)</td>
</tr>
<tr>
<td>Liver cancer HBV (HCV)</td>
<td>405,000 cases (84% in developing countries)</td>
</tr>
<tr>
<td>Liver cancer HCV</td>
<td>232,000 cases (more in developed countries)</td>
</tr>
<tr>
<td>HIV—NHL and Kaposi’s sarcoma</td>
<td>34,500 cases (90% in developing countries)</td>
</tr>
<tr>
<td>EBV—NPC and NHL</td>
<td>150,000 cases (85% in developing countries)</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>190,000 cases (80% in developing countries)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>100,000 cases (95% in developing countries)</td>
</tr>
<tr>
<td>Oral cavity carcinoma</td>
<td>Unknown prevalence (more HPV associated cases in developed countries)</td>
</tr>
</tbody>
</table>


Table 3: Six most common cancers (incidence, age, standardized rates) in both sexes by continent.

<table>
<thead>
<tr>
<th>Africa</th>
<th>Asia</th>
<th>South America</th>
<th>North America</th>
<th>Europe</th>
<th>Oceania</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Breast</td>
<td>Prostate</td>
<td>Prostate</td>
<td>Breast</td>
<td>Breast</td>
</tr>
<tr>
<td>Cervix*</td>
<td>Lung</td>
<td>Breast</td>
<td>Breast</td>
<td>Prostate</td>
<td>Breast</td>
</tr>
<tr>
<td>Prostate Stomach*</td>
<td>Cervix*</td>
<td>Lung</td>
<td>ColoR</td>
<td>Lung</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Liver*</td>
<td>Cervix*</td>
<td>Lung</td>
<td>ColoR</td>
<td>Uterus</td>
<td>Lung</td>
</tr>
<tr>
<td>ColoR</td>
<td>Liver*</td>
<td>ColoR</td>
<td>Uterus</td>
<td>Uterus</td>
<td>Lung</td>
</tr>
<tr>
<td>NHL**</td>
<td>ColoR</td>
<td>Stomach*</td>
<td>NHL**</td>
<td>Cervix*</td>
<td>NHL**</td>
</tr>
</tbody>
</table>

Melanoma: skin melanoma; NHL: non-Hodgkin’s lymphoma; ColoR: colorectal carcinoma; cervix: cervix uteri; uterus: corpus uteri. *Cancers that have a predominantly infectious aetiology. **Cancers of which a component of their aetiology may be associated with infection. Source: GLOBOCAN 2008 [23].

estimated that 86% of cervical cancer incidence and 88% of cervical cancer deaths worldwide occur in under-developed countries [23,30,46].

Helicobacter pylori has been identified as the major cause of not only gastric ulcer and atrophic gastritis but also very likely the cause of most cases of gastric lymphoma and carcinoma. The majority of these malignancies occur in developing countries [28].

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Three parasite species, Schistosoma haematobium, Opisthorchis viverrini, and Clonorchis sinensis, are responsible for the majority of squamous cell carcinoma of the bladder and cholangiocarcinoma in developing countries [28].

2.2. Worldwide distribution

Developing countries already account for half of worldwide cancer [50] and cancers caused by infectious diseases show a disproportionate distribution. Thus cervical cancer is seven times more frequent in sub-Saharan Africa than in western countries (Table 3). The three commonest worldwide cancers, gastric, cervix, and liver, all have infectious etiologies. In the developing world, these comprise two or three of the most common six malignancies, whereas in western countries, only cervical cancer ranks at sixth place in Europe; and none of the other malignancies figure among the most frequent. HCV, however, accounts for the commonest cause of liver cancer in Western countries, primarily due to unsafe parenteral drug usage [48].

3. Mechanisms of oncogenesis

The exact mechanisms underlying oncogenic transformation are not entirely elucidated and likely multicausal (mul-ti-steps). Many mechanisms have been proposed and appear to vary with the agent and specific tumor type.

The oncogenic agent may induce cell wall changes that may lead to cancer, including alteration in the agent itself whereby the viral genome is expressed leading to malignant transformation, either by direct contribution to the tumorigenic phenotype, or by inactivation of tumor suppressor or apoptosis genes [12]. For virus-induced hepatic carcinoma, the virus impairs the ability of the liver
treatable (Table 4). Poor health care is an important risk factor for the development of many infectious malignancies in developing countries, because of lack of access and affordability of preventive or therapeutic measures. Immunization, screening, and treatment may be very cost effective but are unavailable to most [27,42,45,55].

Hepatitis B infection is readily preventable with HBV immunization, and all children of school age should be immunized. In high endemic areas such as some Pacific Islands, where the incidence of chronic hepatitis B exceeded 90% of the population [40,41], the majority caused by vertical transmission, tremendous inroads have been made with universal neonatal immunization without testing the mother. Hepatitis B is known to be sexually transmitted; hence, in non-immunized population, the usual care should be taken for safe sex practices [52].

Hepatitis C is not usually transmissible by sexual contact except perhaps via anal transmission in immunosuppressed recipients [54]. The major route of transmission is parenteral, almost always by intravenous drug use [48] or poor medical technique of improper screening of donors or lack of care such as occurred in the USA during colonoscopy [10] and in France during prostate biopsy [22]. Once the infection is acquired and hepatitis active, while not accessible in developing countries, hepatoma incidence can be decreased by effective viral therapy, most recently with protease inhibitors added to or replacing interferon alpha [37]. A less punitive drug policy whereby drugs may be decriminalized, and/or needle exchange programmes instituted may be effective in controlling some of the “needle acquisition” of HCV.

Human papillomavirus infections can equally be greatly reduced by HPV immunization at an early age [2,32]. Carcinoma of the head and neck and especially the base of the tongue and tonsil has become near-epidemic proportion in the west, and cervical cancer remains one of the greatest causes of morbidity and mortality in developing countries due to lack of medical availability for screening. HPV infections can cause genital warts. Two vaccines are available and all children of both sexes should be immunized. Safe sex practice, no dirty needles.

Human papillomavirus—over 100 serotypes identified, several causing cancer especially types 16 and 18. Types 6 and 11 most commonly cause genital warts. Two vaccines are available and all children of both sexes should be immunized.

Helicobacter pylori—chronic stimulation of lymphoid tissue and irritation causes gastric lymphoma and adenocarcinoma. Screening in endemic areas and treatment with triple or quadruple therapy will eradicate.

Human immunodeficiency virus—predisposes to high-grade lymphomas and expression of other malignancies including HSV type 8 (Kaposi’s sarcoma). Safe sex practise, possible circumcision, sterile drug injections, early treatment with HAART to raise CD4+ count and reduce viral load, pre and post exposure therapy.

Schistosomiasis, Opisthorchiasis, and Clonorchis—bladder and bile duct cancer, respectively. Improving sanitation or screening with early treatment before malignant transformation in endemic areas.

HAART: highly active antiretroviral therapy.
immunization of all children in all localities would prevent the development of the great majority of cervical and oral cavity carcinoma, and screening and therapy for cervical dysplasia in adult women, would prevent a majority of progression to cervical cancers [9]. Screening may be as simple and low cost as using white vinegar to detect cervical dysplasia [51].

_Helicobacter pylori_ has been implicated in the causation of both gastric lymphoma and adenocarcinoma [28]. This carcinoma is far more prevalent in the poorer economies and molecular mechanisms of oncogenesis will add to the understanding of both gastric lymphoma and adenocarcinoma [28]. Improving poor hygienic conditions responsible for acquisition and timely screening and treatment of these infections, long before malignant transformation, would alleviate these malignancies.

For some parasites, a single or short course of albendazole or other medications in an endemic area may prove of value [53].

Human immunodeficiency virus is a worldwide scourge, especially in Sub-Saharan African and Asia where in some countries HIV infection rates are over 30% of the population [35]. Education on prevention does not appear to greatly influence the most at risk groups [7]. However, less than ideal, early therapy does greatly decrease malignant acquisition to near normal levels, and there does appear to be some protective function against transmission by keeping viral loads low as does prophylactic pre and post coital and drug use treatment with anti-viral drugs in high endemic areas [1,5,16,18]. In addition, prophylactic circumcision may have a protective effect against sexual transmission of the disease [4,6,11,26]. In developing countries, screening is far less than ideal, and intensified efforts must identify infected people so that effective regimens can be started and continued.

5. Conclusions

Infection induced malignancy is a worldwide problem especially in the developing world. While there are many causes known, undoubtedly the discovery of more genetic and molecular mechanisms of oncogenesis will add to the growing number of these. However, already in existence today is a substantial burden of preventable malignancies that are being ignored in many parts of the world that require address. The three most common cancers worldwide, caused by infections, can either be prevented by immunization and/or treatment, a very cost-effective undertaking.

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