Global burden of cancers attributable to infections in 2012: a synthetic analysis

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Summary

Background Infections with certain viruses, bacteria, and parasites are strong risk factors for specific cancers. As new cancer statistics and epidemiological findings have accumulated in the past 5 years, we aimed to assess the causal involvement of the main carcinogenic agents in different cancer types for the year 2012.

Methods We considered ten infectious agents classified as carcinogenic to human beings by the International Agency for Research on Cancer. We calculated the number of new cancer cases in 2012 attributable to infections by country, by combining cancer incidence estimates (from GLOBOCAN 2012) with estimates of attributable fraction (AF) for the infectious agents. AF estimates were calculated from the prevalence of infection in cancer cases and the relative risk for the infection (for some sites). Estimates of infection prevalence, relative risk, and corresponding 95% CIs for AF were obtained from systematic reviews and pooled analyses.

Findings Of 14 million new cancer cases in 2012, 2·2 million (15·4%) were attributable to carcinogenic infections. The most important infectious agents worldwide were *Helicobacter pylori* (770 000 cases), human papillomavirus (640 000), hepatitis B virus (420 000), hepatitis C virus (170 000), and Epstein-Barr virus (120 000). Kaposi's sarcoma was the second largest contributor to the cancer burden in sub-Saharan Africa. The AFs for infection varied by country and development status—from less than 5% in the USA, Canada, Australia, New Zealand, and some countries in western and northern Europe to more than 50% in some countries in sub-Saharan Africa.

Interpretation A large potential exists for reducing the burden of cancer caused by infections. Socioeconomic development is associated with a decrease in infection-associated cancers; however, to reduce the incidence of these cancers without delay, population-based vaccination and screen-and-treat programmes should be made accessible and available.

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Introduction

Carcinogenic infections are an important cause of cancer, particularly in less developed countries. Their contribution to the global burden of cancer has been periodically assessed in a series of publications for 1990, 2002, and 2008.[1–3] In 2008, 16·1% of all cancers worldwide were estimated to be attributable to infections, with substantial variation between geographical regions from 3·3% in Australia to 32·7% in sub-Saharan Africa.[1] Here, we update these statistics for the year 2012 using estimates of global cancer incidence from GLOBOCAN 2012[4] and new estimates of population attributable fractions, hereafter referred to as attributable fractions (AFs), for infectious agents derived from a review of reports published in the past 20 years.

Methods

Infectious agents

11 infectious agents have been classified as well established (group 1) carcinogenic agents in human beings by the International Agency for Research on Cancer (IARC): *Helicobacter pylori*, hepatitis B virus (HBV), hepatitis C virus (HCV), HIV type 1 (HIV-1), human papillomavirus (HPV; types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59—known collectively as high-risk types), Epstein-Barr virus (EBV), human herpesvirus type 8 (HHV-8; also known as Kaposi's sarcoma herpesvirus), human T-cell lymphotropic virus type 1 (HTLV-1), *Opisthorchis viverrini*, *Clonorchis sinensis*, and *Schistosoma haematobium*.[5] Among these agents, HIV is unique in attributable risk calculations because, at the best of current knowledge, HIV has been shown to increase cancer risk only in combination with other carcinogenic infectious agents;[5] therefore, we chose to attribute cancers in HIV-positive people to the co-infection. In 2015, we estimated that in the combined antiretroviral therapy era, 40% of cancers occurring in HIV-positive people in the USA are attributable to infections.[6] However, essential information on the number of HIV-infected individuals and cancer incidence among them is lacking in most countries. Consistent with our previous report,[1] we could not accurately estimate the contribution of HIV to the fraction of infection-attributable cancers.

Therefore, we considered the ten infectious agents other than HIV and the associated cancer types (table 1). A few cancer types or subtypes were added to those established

Research in context

Evidence before this study

Evidence on the association between infection and cancer was comprehensively reviewed by an expert working group of the International Agency for Research on Cancer (IARC) in 2009. On the basis of these expert reviews, we published estimates of the global burden of cancer due to infection for the year 2008. To estimate the strength of the associations between specific infection and cancer types in terms of population attributable fraction, we used published meta-analyses where possible and did our own systematic reviews when necessary. Since then, new cancer incidence estimates have become available from GLOBOCAN for the year 2012 and from many new epidemiological studies, including better evidence on the involvement of human papillomavirus in cancers of the head and neck and *Helicobacter pylori* in gastric cancer, notably gastric cardia cancer.

Added value of this study

In this study, we synthesised the available data to present an updated picture of cancer and infection burden worldwide, improving on the previous report by using the most recent data and giving more details of individual country estimates and analysis by level of socioeconomic development. The fraction of all cancers attributable to infection varies greatly between countries, with an important negative association between population attributable fraction and level of socioeconomic development. Despite this association, some highly developed countries continue to show a large burden of infection-attributable cancer because of the long interval between infection acquisition and cancer development.

Implications of all the available evidence

The global burden of infection-attributable cancer is mainly on less developed countries. To reduce this burden, vaccination or screening programmes used in more developed countries should become more widely available.

by an expert working group convened by the IARC.[5] In high-risk areas for *H pylori* infection and gastric cancer in east Asia, evidence shows that a subset of cancers of the gastric cardia arise from severe atrophic gastritis due to *H pylori* along a pathway similar to that of non-cardia gastric cancer.[7] Additionally, recent case series[8,9] that used detection of viral oncoproteins E6 and E7 (ie, PCR with E6 or E7 mRNA, the gold standard for detecting the presence of actively transcribing virus in cancer tissues) now allow the attribution of a small proportion of cancers of the oral cavity and larynx to HPV. Other methodological changes from the previous reports included updating of the fraction of non-cardia gastric cancer attributable to *H pylori* using data from immunoblot, a more sensitive method than ELISA in the detection of *H pylori* infection.[10] We also used data from a meta-analysis of the worldwide distribution of HBV and HCV in hepatocellular carcinoma[11] to obtain improved and separate estimates of liver cancer attributable to the two viruses.

See Online for appendix

Geographical areas

Using data from GLOBOCAN 2012,[4] we estimated the number of new cancer cases due to infections by country and then aggregated these estimates into eight geographical regions based on the UN classification: sub-Saharan Africa, north Africa and west Asia, central Asia, east Asia, Latin America, North America, Europe, and Oceania.[1] We also aggregated results by the 2012 Human Development Index (HDI),[12] a composite indicator of life expectancy, education, and gross domestic product per person. 187 countries were divided by quartiles of HDI distribution into four groups, each with an equal number of countries (although with substantially different population sizes) and labelled as low, medium, high, and very high HDI.[12] We also created a dichotomous HDI classification by combining countries with low and medium HDI into less developed countries, and countries with high and very high HDI into more developed countries. In some instances, China was shown separately from other medium-HDI countries because of the large size of its population and cancer burden (accounting for 3·1 million [60%] of the 5·2 million cancer cases in medium-HDI countries)[4] and because changes in HDI methodology have classified China as a high-HDI country since 2014.[13]

Statistical analysis

The AF for carcinogenic infections is the proportion of new cancer cases that would have been prevented in a population if all infections had been avoided or successfully treated before they caused cancer. Briefly, for HPV in cervical cancer, HTLV-1 in adult T-cell leukaemia and lymphoma, and HHV-8 in Kaposi's sarcoma, 100% of cancers are attributed to the infection (table 1; see appendix for detailed methods).[5] For HPV at other cancer sites and EBV-related cancers, the prevalence of viral transcripts in tumour cells in cases from case series and case-control studies was used to estimate the AF. For *H pylori*, HBV, and HCV, AF estimates were based on the prevalence in cases adjusted by the relative risk as previously described.[1] For rare cancers caused by parasites in endemic areas, specific methods were used as before,[1] because of the dearth of available data (appendix).

We derived 95% CIs for the AF estimates from random-effects meta-analysis of infection prevalence in case series (HPV and EBV). When the AF also depended on relative risk estimates (ie, for *H pylori*, HBV, and HCV), the 95% CI accounted for the uncertainty in both prevalence