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

Martyn Plummer, Catherine de Martel*, Jerome Vignat, Jacques Ferlay, Freddie Bray, Silvia Franceschi*

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

	Type of studies used for AF estimation	Laboratory method	Population and AF (95% CI)
Helicobacter pylori*			
Non-cardia gastric carcinoma† (C16.1–9)	Cohort	Immunoblot	World: 89% (79–94)
Gastric cardia carcinoma† (C16.0)	Cohort	ELISA	East Asia: 29% (10–45)
Gastric non-Hodgkin lymphoma† (C82–85, C96)	Cohort and case-control	ELISA	World: 74% (43–86)
Hepatitis B virus*			
Liver cancer (C22)	Cohort, case-control, and case series	HBsAg	World: NS‡
Hepatitis C virus*			
Liver cancer (C22)	Cohort, case-control, and case series	ELISA (second or third generation)	World: NS‡
Non-Hodgkin lymphomas† (C82–85, C96)	Cohort and case-control	ELISA (second or third generation)	Low-risk countries: 1·7% (1·5–2·1) High-risk countries: 9·8% (8·2–12·0) Egypt: 24% (20–28)
HPV (high-risk types)§			
Cervix uteri carcinoma (C53)	Case-control	DNA PCR	World: 100%
Penile carcinoma† (C60)	Case-control	DNA PCR	World: 51% (47–55)
Anal carcinoma† (C21)	Case-control	DNA PCR with $p16^{INK4A}$	World: 88% (85–91)
Vulvar carcinoma† (C51)	Case-control	DNA PCR with $p16^{INK4A}$	Age 15–54 years: 48% (42–54) Age 55–64 years: 28% (23–33) Age ≥65 years: 15% (11–18)
Vaginal carcinoma† (C52)	Case-control	DNA PCR	World: 78% (68–86)
Carcinoma of the oropharynx, including tonsils and base of tongue† (C01, C09–10)	Case-control	PCR for DNA and HPV E6/E7 mRNA expression	North America: 51% (41–57) Northwest Europe: 42% (34–47) East Europe: 50% (39–57) South Europe: 24% (17–30) China: 23% (17–27) Japan: 46% (39–59) India: 22% (5–44) South Korea: 60% (46–70) Australia: 41% (32–47) Elsewhere: 13% (5–23)
Cancer of the oral cavity† (C02–06)	Case-control	PCR for DNA and HPV E6/E7 mRNA expression	World: 4·3% (3·2–5·7)
Laryngeal cancer (C32)	Case-control	PCR for DNA and HPV E6/E7 mRNA expression	World: 4·6% (3·3–6·1)
EBV§			
Hodgkin's lymphoma (C81)	Cohort and case-control	In-situ hybridisation of EBV-encoded small RNAs and EBV latent membrane protein 1	Africa: 74% (65–82) Latin America: 60% (54–67) Asia: 56% (52–60) Europe: 36% (32–39) North America: 32% (25–39) Australia: 29% (10–58)
Burkitt's lymphoma† (C83.7)	Case-control and case series	In-situ hybridisation of EBV-encoded small RNAs and Epstein-Barr nuclear antigen 4	Sub-Saharan Africa: 100% USA and Europe: 20% Elsewhere: 30%
Nasopharyngeal carcinoma (C11)	Case-control and case series	In-situ hybridisation of EBV-encoded small RNAs	High-incidence countries: 100% Low-incidence countries: 80%
Human herpesvirus type 8§			
Kaposi's sarcoma (C46)	Not applicable	DNA PCR	World: 100%
Human T-cell lymphotropic virus*			
Adult T-cell leukaemia and lymphoma† (C91.5)	Not applicable	Immunoblot	World: 100%
Opisthorchis viverrini* and *Clonorchis sinensis			
Bile duct cancer† (C22.1)	Case-control	Various	Endemic areas in southeast Asia: NA¶
Schistosoma haematobium			
Bladder carcinoma (C67)	Case-control	Various	Endemic areas in Africa: 41% (36–48)

AF=attributable fraction. HPV=human papillomavirus. EBV=Epstein-Barr virus. *In sera. †These subtypes were not directly available in GLOBOCAN 2012; therefore, data from the Cancer Incidence in Five Continents (CI5-X) database were used to estimate the corresponding incidence. ‡NS=not shown because country-specific estimates were used (appendix). §In cancer tissue. ¶NA=not available because a different method was used to calculate AF.

Table 1: **General methods for the calculation of the AFs of infectious agents, by cancer type (International Classification of Diseases-10 code)**

and relative risks. These estimates were combined using a Bayesian perspective and calculated using Monte Carlo methods and R software (version 3.1.1; appendix pp 1–2).[14]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Number of new cases	Number attributable to infection	Attributable fraction (%)
Worldwide	14 000 000	2 200 000	15·4%
Africa			
Sub-Saharan Africa	630 000	200 000	31·3%
North Africa and west Asia	540 000	70 000	13·1%
Asia			
Central Asia	1 500 000	290 000	19·4%
East Asia	4 900 000	1 100 000	22·8%
America			
Latin America	1 100 000	160 000	14·4%
North America	1 800 000	72 000	4·0%
Europe	3 400 000	250 000	7·2%
Oceania	160 000	7600	4·9%
Human Development Index			
Very high	5 700 000	430 000	7·6%
High	2 200 000	290 000	13·2%
Medium	5 200 000	1 200 000	23·0%
Low	940 000	240 000	25·3%
Level of development			
More developed regions	7 900 000	730 000	9·2%
Less developed regions	6 200 000	1 400 000	23·4%

Numbers of cases rounded to two significant figures.

Table 2: **Number of new cancer cases in 2012 attributable to infectious agents, by geographical region and level of development**

Results

Of the estimated 14 million new cancer cases worldwide in 2012, 2·2 million (15·4%) were attributable to infection (table 2). AFs varied by region from 4·0% in North America to 31·3% in sub-Saharan Africa. AF was highest in low-HDI countries and medium-HDI countries, and lowest in countries with very high HDI (table 2). Two-thirds of infection-attributable cancers (1·4 million cases) occurred in less developed countries (table 2).

In 2012, the AFs of infection-related cancers were less than 5% in the USA, Canada, Australia, New Zealand, and some countries in northern and western Europe, but more than 40% in several countries in sub-Saharan Africa and in Mongolia (figure 1). The AF by country ranged from 3·6% in Sweden to more than 50% in Malawi and Mozambique (appendix pp 22–26).

H pylori, HPV, HBV, and HCV were together responsible for 2·0 million new cancer cases worldwide in 2012 (table 3), with *H pylori* being the largest contributor. The high burden of HPV-attributable cancer (predominantly cervical cancer) in women almost exactly counterbalanced the excess in men for all other infections, so that overall the numbers of cancers attributable to all infections were similar for both sexes (1·1 million each; table 3). According to GLOBOCAN 2012,[4] 64% of all cancers occur before age 70 years (which is the same age limit that has been used by WHO since 2010[15] to define premature death from non-communicable diseases), but the corresponding proportion of such cancers was considerably higher for cancers caused by HPV (86%), EBV (88%), and HHV-8 (90%) than for other cancers, such as those caused by *H pylori* (57%; table 3).

The burden of cancers attributable to infections was dominated by cancers of the stomach, liver, and cervix

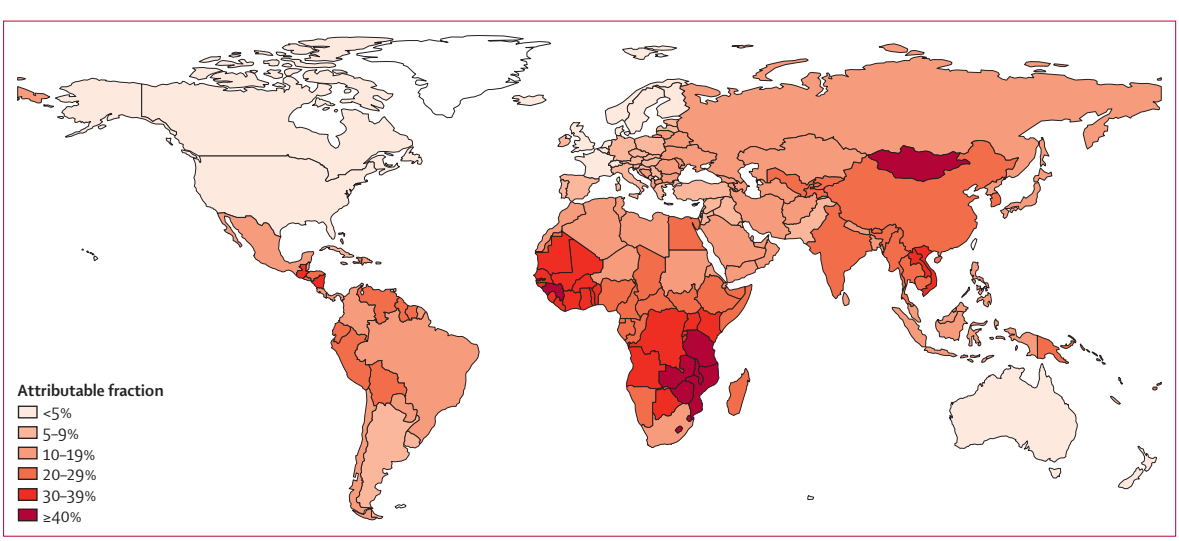

Figure 1: **Attributable fraction of cancer related to infection, 2012**

	Number of new cases	Proportion of new cases attributable to each infectious agent (%)	Number of new cases attributable to infection by sex		Number of new cases attributable to infection by age group		
			Males	Females	<50 years	50–69 years	≥70 years
Helicobacter pylori	770 000	35·4%	500 000	270 000	91 000	340 000	330 000
Human papillomavirus	640 000	29·5%	66 000	570 000	270 000	280 000	90 000
Hepatitis B virus	420 000	19·2%	300 000	120 000	84 000	190 000	140 000
Hepatitis C virus	170 000	7·8%	110 000	55 000	26 000	76 000	66 000
Epstein-Barr virus	120 000	5·5%	80 000	40 000	61 000	44 000	14 000
Human herpesvirus type 8	44 000	2·0%	29 000	15 000	32 000	7600	4500
Schistosoma haematobium	7000	0·3%	4900	2200	1300	3700	2100
Human T-cell lymphotropic virus, type 1	3000	0·1%	1700	1200	630	1200	1200
Opisthorchis viverrini or *Clonorchis sinensis*	1300	0·1%	820	470	130	670	490
All infectious agents	2 200 000	100·0%	1 100 000	1 100 000	570 000	950 000	650 000

Numbers of cases rounded to two significant figures.

Table 3: **Number of new cancer cases in 2012 attributable to infection, by infectious agent**

(table 4)—ie, the fifth, sixth, and seventh most common cancers worldwide, respectively, after lung, breast, colorectal, and prostate cancers.[4] These cancer types also had very high infection-related AFs: 89·0% of non-cardia gastric cancer was attributable to *H pylori*, 73·4% of liver cancer was attributable to HBV and HCV (a small number of intrahepatic bile duct cancers caused by liver flukes were also included), and 100·0% of cervical cancer was caused by HPV. The global burden of HPV-attributable cancer other than cervical cancer (113 000 cases) was substantially lower than that of cervical cancer (530 000 cases).

Figure 2 shows the total number of cancer cases by cause, the burden of cancer attributable to infection by HDI (AF), and the proportion of cases attributable to each infectious agent. Low-HDI countries were the only category that had a high proportion of HHV-8-related cancers (14%, compared with 2% worldwide). Apart from the burden of HHV-8-related cancers, low-HDI and medium-HDI countries (excluding China) had a similar range of infection-attributable cancers. China had a unique pattern of such cancers, with a low proportion of HPV-attributable cancers and a high proportion of cancers caused by HBV and *H pylori*. *H pylori* also had an important contribution to the cancer burden in countries with high and very high HDIs. Whereas HBV predominates over HCV as a cause of liver cancer in low-HDI and medium-HDI countries, HBV and HCV have similar contributions to the cancer burden in high-HDI countries, and HCV predominates in countries with very high HDI.

In both less developed and more developed countries, the AFs were generally higher in younger age groups, peaking in people aged 40–45 years, except for women in more developed countries where the peak was in people younger than 40 years (figure 3).

	Number of new cases	Number of new cases attributable to infectious agents	Attributable fraction
Carcinoma			
Non-cardia gastric	820 000	730 000	89·0%
Cardia gastric	130 000	23 000	17·8%
Liver	780 000	570 000	73·4%
Cervix uteri	530 000	530 000	100·0%
Vulva	34 000	8500	24·9%
Anus	40 000	35 000	88·0%
Penis	26 000	13 000	51·0%
Vagina	15 000	12 000	78·0%
Oropharynx	96 000	29 000	30·8%
Oral cavity	200 000	8700	4·3%
Larynx	160 000	7200	4·6%
Nasopharynx	87 000	83 000	95·5%
Bladder	430 000	7000	1·6%
Lymphoma and leukaemia			
Hodgkin's lymphoma	66 000	32 000	49·1%
Gastric non-Hodgkin lymphoma	18 000	13 000	74·1%
Burkitt's lymphoma	9100	4700	52·2%
HCV-associated non-Hodgkin lymphoma	360 000	13 000	3·6%
Adult T-cell leukaemia and lymphoma	3000	3000	100·0%
Sarcoma			
Kaposi's sarcoma	44 000	44 000	100·0%
All infection-related cancer types	3 800 000	2 200 000	56·5%

Numbers rounded to two significant digits. HCV=hepatitis C virus.

Table 4: **Number of new cancer cases in 2012 attributable to infectious agents, by cancer type**

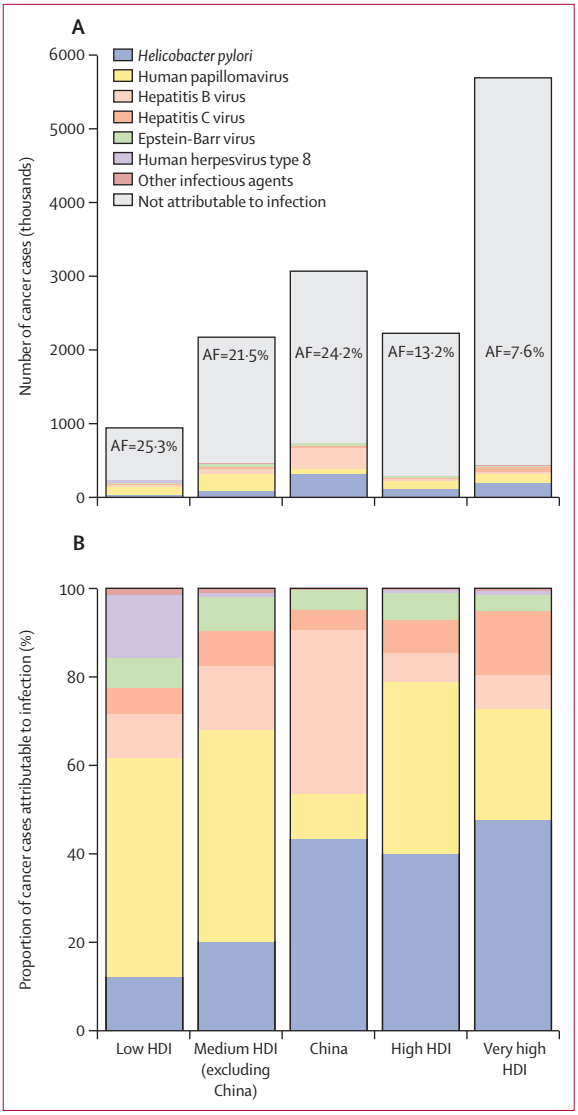

Figure 2: **(A) Total number of cancer cases (by cause) and (B) proportion of cancer cases attributable to different infectious agents, 2012**
AF=attributable fraction. HDI=Human Development Index.

Discussion

In 2012, around 15% of cancer cases worldwide were attributable to infectious agents. Two-thirds of infection-attributable cancers occurred in less developed countries, in which infections accounted for nearly one in four cancers. The main infectious agents contributing to the cancer burden were *H pylori*, HPV, HBV, and HCV, which together accounted for 92% of all infection-attributable cancers worldwide.

H pylori was the most important infectious cause of cancer in countries with high and very high HDIs. Of note, the very high incidence of stomach cancers in Japan and Korea is accompanied by an unusually good prognosis, because of the intensive search for gastric lesions through national endoscopic screening programmes.[16]

The ratio of liver cancers attributable to HBV and HCV varied substantially with HDI. Although HBV was more important than HCV as a cause of cancer in low-HDI and medium-HDI countries, the opposite was true in countries with high and very high HDIs because of the especially early spread of HCV in some countries with very high HDI (eg, in 1930s in Japan) and the diminishing prevalence of HBV with increasing HDI (figure 2). Of note, the prevalence of HCV in the general population varied greatly between countries because of differences in the presence and timing of mass episodes of iatrogenic transmission and, more recently, intravenous drug use.[11,17]

HPV caused more than half of all infection-attributable cancers in women worldwide. In low-HDI countries, it accounted for half of infection-attributable cancers in both sexes combined. Elevated rates of cervical cancer resulted from poor screening and treatment of precancerous cervical lesions, in combination with high prevalence of HPV and HIV infections.[18]

HHV-8 accounted for only 2% of infection-attributable cancers worldwide, but in low-HDI countries this proportion was 14%. Kaposi's sarcoma mainly affects individuals younger than 50 years and continues to be a major public health concern in Africa, where HHV-8 is endemic and large numbers of HIV-infected individuals have late or no access to combined antiretroviral therapy.[19]

This Article is part of a periodic series of publications assessing the burden of cancer due to infection.[1–3,6] Worldwide, the AF for 2012 (15%) is similar to previous estimates for 2008 (16%),[1] 2002 (18%),[2] and 1990 (16%).[3] However, these estimates are not directly comparable. Each publication in this series represents a snapshot of the state of knowledge at the time of publication, and the cancer data sources and methods have both evolved with time.

Major improvements over the previous report for 2008 include AF estimates for individual countries, the re-assessment of the AFs of some major infections, and the addition of confidence intervals. We were able to separate data for liver cancers attributable to HBV and HCV on the basis of results from a systematic review in 2015.[11] Other reviews in the past 5 years have allowed more accurate estimates of AFs using, for instance, prospective studies of *H pylori* and non-cardia gastric cancer[10] and updated meta-analyses of Epstein-Barr virus infection prevalence in Hodgkin's lymphoma.[20] For HPV in cancers of the head and neck, multinational case series[8,9] have added valuable additional evidence of causality (appendix pp 5–6, 13–15).

An important improvement is the calculation of country-level and HDI-level estimates of the burden of cancer attributable to infection. The distinct patterns of cancer incidence by HDI were previously analysed by Bray and colleagues,[21] who noted that rapid societal and socioeconomic transition in many countries means that any reductions in infection-related cancers are offset by an increasing number of new cases that are more associated with reproductive, dietary, and hormonal

factors. AFs of cancers caused by infection were low in countries with very high HDIs, but exceptions exist, mainly because of a large burden of gastric and liver cancer in, for example, Japan and Korea (AFs around 20% in both countries). Other countries with very high HDIs, notably those in Latin America and the Middle East, had AFs of more than 10% (appendix pp 22–26). These examples show that a substantial delay might exist between socioeconomic development and reduction in the proportion of infection-attributable cancers.

The main limitations of our study are associated with the scarcity of representative data for infection prevalence and of high-quality cancer registration in many populations, as well as the difficulty in characterising the full degree of uncertainty of our estimates. The 95% CIs for AF estimates in table 1 represent the substantial strength of the association of individual infections with specific cancer types from meta-analyses or pooled data, but associations with other less well studied cancer types or subtypes remain less clear. For example, non-Hodgkin lymphoma cases were considered together as attributable to HCV, although the association might vary with histological subtypes. Furthermore, few data exist for EBV presence by non-Hodgkin lymphoma subtype in immunocompetent populations, even though 5–10% of all non-Hodgkin lymphoma cases might be attributable to EBV (appendix p 7). Another possible example of underestimation of the AFs is those for *H pylori* and gastric cardia cancer outside east Asia, the only region where relevant data were available. Most importantly, the numbers of cases attributable to infection were derived from incidence estimates from GLOBOCAN 2012,[4] which does not give a quantitative assessment of uncertainty. For individual countries, however, the alphanumeric quality score from GLOBOCAN—which describes the quality and coverage of incidence data (A–G) and the accuracy of the methods used to estimate incidence (1–9; appendix p 26)—provides a useful qualitative assessment of the uncertainty of the incidence estimates. Countries with the highest score (A1) should generally have accurate incidence estimates, whereas estimates for countries with the lowest score (G9) represent a best guess in the complete absence of country-specific data. Special caution should be used for countries that showed very high AFs for infection, as this finding might be due to incomplete registration of cancers that are not associated with infections.[22]

Our findings suggest that the potential for reducing the burden of cancer is large. However, the proportion of preventable cancers might be considerably lower than the AF and will depend on the resources available for the implementation of large-scale interventions. It is encouraging that highly effective prophylactic vaccines (against HBV and HPV) and screen-and-treat strategies (for HPV and HCV) exist and are being implemented in some countries.[18,23]

As of 2014, 184 countries had incorporated the HBV vaccine as an integral part of their national infant

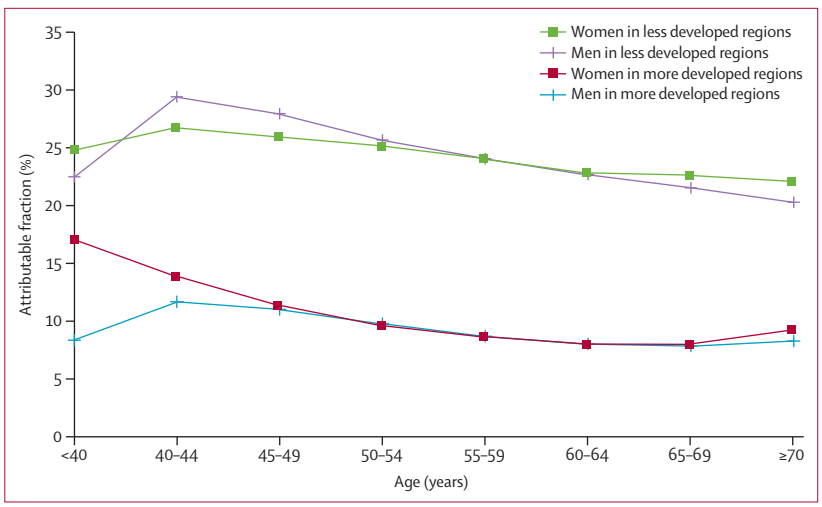

***Figure 3*: Proportion of cancer cases in 2012 attributable to infection, by sex, age group, and development status**

immunisation programmes.[24] Vaccination has been shown to prevent liver cancer in children and young adults in Taiwan since it was introduced in 1984.[25] The timely delivery of a vaccine dose within 24 h of birth has become a performance measure for HBV immunisation programmes.[26] A birth dose had been introduced in 96 countries by 2014, and the global coverage was estimated at 38%, reaching 80% in the western Pacific, but only 10% in Africa.[24]

In the past 10 years, most countries in Europe and the Americas, as well as Australia, have introduced national HPV vaccination programmes targeting adolescent girls, but coverage varies vastly from less than 30% to more than 80%.[27] Large efforts are necessary to improve coverage and bring HPV vaccination to less developed countries in sub-Saharan Africa and Asia. Vaccination programmes with a coverage of at least 80% have been shown to be achievable in less developed countries such as Rwanda and Bhutan. Gavi, The Vaccine Alliance, is bringing relatively low-cost HPV vaccines to dozens of additional countries with few financial resources.[27] The screening of women older than 30 years, possibly with affordable rapid HPV tests, has also been endorsed by WHO.[28]

A national HCV screen-and-treat programme of individuals born between 1945 and 1965 has been launched in the USA, taking advantage of highly effective but still very expensive new antiviral treatments.[23] A global reduction in liver cancer caused by HCV and HBV will depend on the identification and appropriate referral of individuals at risk, and on the widespread delivery and affordability of these new treatments in different countries.[29]

Early initiation of combined antiretroviral therapy is associated with massive reductions in the risk of developing Kaposi's sarcoma.[30] The 2015 WHO clinical guidelines[31] recommend the initiation of combined anti-retroviral therapy in all HIV-positive individuals

regardless of clinical stage or CD4-positive cell count. This strategy has the potential to prevent most cases of Kaposi's sarcoma and possibly a fraction of HPV-associated cancer in sub-Saharan Africa.[32]

Last but not least, our results highlight the continuing importance of *H pylori* as an infectious cause of cancer in many world regions, including some more developed countries. Anti-*H pylori* therapy has been overlooked as a strategy for cancer prevention because of concerns about the widespread use of antibiotics and the possibility that *H pylori* eradication might increase the risk of oesophageal cancer.[7] Nevertheless, an IARC working group has recommended that countries explore the possibility of introducing population-based *H pylori* screening and treatment programmes for gastric cancer control.[33]

In conclusion, carcinogenic infections remain an important cause of cancer worldwide, especially in less developed countries. For several of the infections we assessed, with the exception of sexually transmitted HPV,[18] socioeconomic development is associated with a reduction in transmission or in progression to cancer. However, socioeconomic development is not sufficient to reduce the infection-associated cancer burden, unless population-based interventions similar to those implemented in some countries with very high HDIs are prioritised and made cost-effective in the rest of the world.

Contributors

SF, MP, and CdM conceived and designed the study. JF provided cancer incidence estimates adapted from the GLOBOCAN 2012 database. MP, JV, and FB collected and analysed the data collection. CdM and MP drafted the manuscript. All authors contributed to the interpretation of data and approved the final manuscript.

Declaration of interests

We declare no competing interests.

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