Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide

Delphine Maucort-Boulch1-2-3-4, Catherine de Martel5, Silvia Franceschi5 and Martyn Plummer5

1 Service de Biostatistique et Bioinformatique, Hospices Civils de Lyon, Lyon, France
2 Université de Lyon, Lyon, France
3 Université Lyon 1, Villeurbanne, France
4 CNRS, UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, Equipe Biostatistique-Santé, Villeurbanne, France
5 International Agency for Research on Cancer, Lyon, France

High-quality data on liver cancers by probable cause are scarce in many regions of the world. The United Nations recently set a goal of eliminating viral hepatitis as a major public health threat by 2030. We aimed to estimate the number of new cases of cancers attributable to hepatitis B virus (HBV) and hepatitis C virus (HCV) at a global, regional and country level, and by development status. We used data on the prevalence of HBV and HCV in hepatocellular carcinoma from a systematic review including 119,000 cases in 260 studies covering 50 countries. A statistical model was constructed to extrapolate empirical data to countries without prevalence data. Country-specific numbers of liver cancer cases attributable to HBV and HCV were calculated using data from GLOBOCAN 2012. Globally, 770,000 cases of liver cancer occurred worldwide in 2012, of which 56% (95% CI: 52–60) were attributable to HBV and 20% (95% CI: 18–22) to HCV. Currently, HBV causes approximately two out of three cases of liver cancer in less developed countries but one in four cases in more developed countries and shows a much higher degree of geographical aggregation in Eastern Asia and sub-Saharan Africa than HCV. These estimates help set priorities for liver cancer prevention. High-coverage HBV vaccination will be transformational in HBV-endemic countries but the prevention of HCV transmission and the treatment of chronic carriers of both viruses requires new scalable solutions.

Liver cancer is the second most common cause of cancer death worldwide after lung cancer.1 Most primary liver tumors are hepatocellular carcinoma (HCC) with the exception of some areas of South-Eastern Asia where intrahepatic bile duct cancer is also common due to the endemic presence of liver flukes.2 Several risk factors for the development of HCC have been identified: among these, chronic infections with hepatitis B and C viruses (HBV and HCV) are largely predominant, although their relative contribution shows important geographical variations.3 Other risk factors include alcohol consumption, cigarette smoking, diabetes, overweight and aflatoxin B1.4,5

As part of an ongoing project to estimate the global burden of cancer attributable to infections, we estimated the number of incident liver cancers attributable to HBV and HCV worldwide. Our findings have been briefly summarized in an article on the global burden of cancer attributable to all carcinogenic infections.6 Here, we report estimates for HBV and HCV in fine-grained detail. In particular, we give estimates of the attributable fraction (AF) and its confidence

Key words: liver neoplasms, hepacivirus, epidemiology, attributable fraction

Abbreviations: AF: attributable fraction; ASR: age standardized incidence rate; CI: confidence interval; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; HDI: human development index; pc: prevalence in cases; RR: relative risk

Additional Supporting Information may be found in the online version of this article.

Conflict of interest: The authors declare that they have no conflicts of interest.

Grant sponsor: Fondation de France; Grant number: 00039621; Grant sponsor: Bill & Melinda Gates Foundation; Grant number: OPP1053353

DOI: 10.1002/ijc.31280

This is an open access article distributed under the terms of the Creative Commons Attribution IGO License IARC’s preferred IGO license is the non-commercial: https://creativecommons.org/licenses/by-nc/3.0/igo/legalcode which permits non-commercial unrestricted use, distribution and reproduction in any medium, provided that the original work is properly cited. In any reproduction of this article there should not be any suggestion that IARC/WHO or the article endorse any specific organization or products. The use of the IARC/WHO logo is not permitted. This notice should be preserved along with the article’s URL.

History: Received 11 Dec 2017; Accepted 22 Jan 2018; Online 31 Jan 2018

Correspondence to: Dr Martyn Plummer, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, Tel.: +33-472-73-84-46, Fax: +33-472-73-83-45, E-mail: plummerm@iarc.fr

Int. J. Cancer: 142, 2471–2477 (2018) © 2018 International Agency for Research on Cancer (IARC/WHO); licensed by UICC
Liver cancer attributable to hepatitis viruses worldwide

What’s new?
To facilitate priority setting for liver cancer prevention, more data are needed on attributable causes of liver malignancy. Here, the prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) in hepatocarcinoma was determined based on systematic review of data from 50 countries, with liver cancer cases attributable to the viruses calculated using GLOBOCAN 2012 data. The results show that of 770,000 liver cases reported in 2012, more than half were attributed to HBV, while one-fifth were associated with HCV. The contribution of the two viruses to liver cancer varied significantly by development status and region.

Methods
Estimates of the burden of liver cancer due to HBV and HCV were obtained by combining three data sources: prevalence estimates of HBV and HCV in HCC cases; relative risks of HCC given HBV and HCV infection; incidence of liver cancer in each country in the two sexes combined.

Data on the prevalence of HBV and HCV in HCC come from a systematic review including 119,000 cases in 260 studies published between 1989 and 2014 covering 50 countries. Eligible studies had seroprevalence data on hepatitis B surface antigen (HBsAg) and anti-HCV antibodies in at least 20 HCC cases. Cases were classified as one of HBV-only, HCV-only, dual infection or no viral involvement. For countries with sufficient data to give separate prevalence estimates for the periods before and after the year 2000, only data from the latter period were used in the current analysis.

A statistical model was fitted to the prevalence data. See Supporting Information, Methods S1 for details. Briefly, a multinomial regression model was used with a separate intercept for nine geographical regions. Random effects at two levels represented variation in prevalence between countries within the same region and variation between different studies in the same country. This model was then used to extrapolate prevalence estimates in countries with no data. This model has two key features. First, the use of a multinomial outcome with four levels (HBV-only, HCV-only, dual infection or no infection) avoids making strong assumptions about the relationship between HBV prevalence and HCV prevalence, or about the proportion of joint infections. Second, the use of random effects accounts for the observed sources of variation in the prevalence data. This variation is fully accounted for in the extrapolation to countries with no prevalence data and is incorporated into the confidence intervals for the country-specific and regional AF estimates.

No HBV and HCV prevalence data in cases were available for Oceania in our review. For New Zealand, we used a prevalence study that did not meet the standards for our systematic review but provided data on HBV prevalence. For Australia and for countries in Melanesia, Micronesia and Polynesia, no data were available and therefore we do not present results for these countries.

Estimates of HBV and HCV prevalence were combined with a risk model for HCC to obtain AF estimates for each of 184 countries using the formula of Bruzzi et al.

\[ \text{AF}=p_c \frac{(\text{RR}-1)}{\text{RR}} \]

where RR is the relative risk and \( p_c \) is the prevalence in cases.

Relative risk (RR) estimates of 23.4 (95% CI 17.2–31.7) for HBV-only and 27.6 (95% CI 19.8–38.4) for HCV-only were obtained from a systematic review and meta-analysis of HCC. For joint infection, an additive excess relative risk model was assumed, that is, an RR of 23.4 + 27.6 – 1 = 50, consistent with the RR of 51.1 (95% CI 33.7–77.6) for joint infection reported by the above meta-analysis. Under this model, attributable fractions are additive, so that attributable cases can be partitioned exactly between HBV and HCV. The 95% CIs for these AFs combine the uncertainty in the prevalence estimate and the RR estimates.

Country-specific AF estimates were multiplied by estimated numbers of cases of liver cancer from GLOBOCAN 2012 to give the estimated number of cases attributable to HBV and HCV in each country. GLOBOCAN is a periodic series of estimates of cancer incidence and mortality worldwide for 27 major cancers and 184 countries worldwide based on best available data on cancer incidence and mortality at the national level. For details of the methodology, see Ferlay et al. GLOBOCAN does not provide specific incidence estimates for HCC (International Classification of Diseases - ICD-10 code C22.0). We use the GLOBOCAN estimates for cancer of the liver and intrahepatic bile ducts (C22) on the basis that the vast majority of these will be HCC. Estimates of attributable incidence of HCC were aggregated by geographic region and by development status. The human development index (HDI)—a composite indicator of education, gross domestic product per person and life expectancy—was used to classify countries as “less-developed” (low and medium HDI) or “more developed” (high and very high HDI). As GLOBOCAN provides only a point estimate of cancer incidence without a quantitative assessment of uncertainty, it was not possible to account for the full uncertainty in the estimated number of cases attributable to HBV and HCV. These are therefore presented without 95% CIs.
To show the burden of HBV and HCV in liver cancer at a country level, two sets of world maps were produced. The first set (Fig. 1) presents estimated AFs separately for HBV (1a) and HCV (1b). The second set (Fig. 2) shows age standardized incidence rate (ASR) for liver cancer attributable to HBV (2a) and HCV (2b) and liver cancer attributable to other causes (2c), when cancers attributable to HBV and HCV have been removed. These encompass liver cancers attributable to other risk factors in the absence of HBV and HCV infection, such as alcohol, diabetes, obesity, metabolic syndrome, aflatoxin B1 and also liver flukes in endemic regions.4,5

Results
Globally 770,000 cases of liver cancer occurred worldwide in 2012, of which 430,000 are estimated to be attributable to HBV and 150,000 attributable to HCV (Table 1), corresponding to a global AF of 56% (95% CI: 52–60) and 20% (95% CI: 18–22) respectively. Distinct patterns are seen by development status. In less developed countries, where the majority of liver cancer cases occur, the AFs are 67% (95% CI 61–72) for HBV and 12% (95% CI 10–15) for HCV. In more developed countries, the AFs are 23% (95% CI: 20–27) and 44% (95% CI: 38–49) for HBV and HCV, respectively.

Table 1 also shows the variation by geographic region. The highest AF for HBV is 69% (95% CI: 63–74) in Eastern Asia, a high-endemic area for the infection. High AFs for HBV are also observed for New Zealand (49%), sub-Saharan Africa (50%) and Western and Central Asia (46%), where the CIs are all consistent with over 50% of liver cancers being attributable to HBV. The highest AFs for HCV are in North Africa (79%: 95% CI 69–86) and Northern America (59%: 95% CI 37–79).

Figure 1 shows the international variation in AF at the country level (the corresponding estimates and 95%CIs are given in the Supporting Information, Table S1. The AF for HBV (Fig. 1a) shows a high degree of geographical aggregation; the AF for any given country is generally similar to its neighboring countries. In addition to the regional results highlighted in Table 1, For HCV, the global geographical pattern is different (Fig. 1b) with less geographical aggregation, reflecting the different sources and timing of HCV
transmission. Countries with AF over 50% for HCV are all countries in the North African region as well as Brazil, Italy, Japan, Mexico, Pakistan and the USA (Supporting Information, Table S1).

Figure 2 shows the variation in liver cancer ASR attributable to HBV (Fig. 2a), HCV (Fig. 2b) and other causes (Fig. 2c). Although based on AF in Figure 1, Figure 2 also takes into account the enormous variation in country-specific liver cancer burden. Figure 2a shows the high ASR of liver cancer due to HBV in East and South-East Asia and in West Africa. Figure 2b shows that the highest ASR of liver cancer due to HCV (>7.5 per 100,000) is only found in Egypt and...
Figure 2c shows that worldwide, except in Mongolia and South East Asia, the ASR attributable to other causes also varies substantially but does not reach levels as high as those seen for HBV and HCV.

Discussion

We provide estimates of the global burden of liver cancer due to HBV and HCV, using a statistical model to extrapolate available prevalence data to countries with little or no empirical data. While there are many ways to do this extrapolation, the key advantage of using a statistical model is that the uncertainty of the extrapolation is incorporated into our final estimates of AF. This is reflected in the AF estimates for individual countries (Supporting Information, Table S1), where the 95% CIs are larger in countries for which HBV/HCV prevalence data are not available. For example, 95% CIs for the AF in Mexico, where only one small prevalence study was included in the systematic review, are (5–40%) for HBV and (28–83%) for HCV, reflecting substantial uncertainty. Aggregate AF estimates such as those presented in Table 1 are estimated more precisely.

Our results show the contrasting roles of HBV and HCV in less-developed and more-developed countries. Currently, HBV causes 2/3 cases of liver cancer in less-developed countries but only 1/4 cases in more-developed countries. HCV is a relatively less important cause of liver cancer in less-developed countries where it causes 1/8 cases, but nearly 1/2 cases in more-developed countries.

In contrast to other estimates of the disease burden based on prevalence of viral markers in the general population, our estimates are based on prevalence in HCC cases. We consider that this is the best approach to estimate AF for carcinogenic infections for two reasons. First, unselected consecutive HCC cases are more likely to represent the current picture of the disease in a given area than surveys undertaken in population samples, which are often biased in unpredictable ways as they tend to oversample low-risk (i.e., pregnant women, blood donors) or high-risk groups (e.g., prisoners, homeless people, injecting drug users or migrants from high-risk countries). Second, HBV and HCV are strong risk factors for liver cancer (RR >20 for both viruses), so the prevalence in cases is a good approximation of the AF when using the formula conceived for case–control studies (see Methods).

Figures 1 and 2 show two different but equally important ways to summarize the worldwide variation in liver cancers attributable to HBV and HCV. The AFs show the relative importance of HBV and HCV without reference to the incidence of liver cancer, whereas the attributable ASRs allow international comparison of liver cancer burden by cause after allowance for population age structure. The complementarity of the two approaches can be appreciated, for instance, in North Africa. Although HCV is a relatively important cause of liver cancer across the whole of North Africa (Fig. 1b), it only causes a huge burden of liver cancer in Egypt (Fig. 2b) due to the very high number of individuals who acquired HCV during mass-injection campaigns against Schistosoma haematobium in previous decades. Similarly,
Liver cancer attributable to hepatitis viruses worldwide

50% AF for HBV is associated with an enormous HCC burden in East Asia and sub-Saharan Africa.

The interpretation of the high ASR estimates attributable to causes other than HBV and HCV is obviously more difficult. Notably the highest ASRs for liver cancer due to other causes (ASR > 6.0/100,000) are typically found in HBV-endemic regions of Asia and Africa. In these countries, it only takes a small underestimation of the AF for HBV to inflate ASRs from other causes. Indeed, occult HBV infection may lead to an underestimation of the AF for HBV based on HBsAg prevalence. In addition, in South East Asia, China and the Republic of Korea, liver cancer includes a high fraction of cholangiocarcinoma and an ill-measured fraction of HCC caused by liver flukes.\(^7\) In more developed countries, although the ASRs for liver cancer attributable to causes other than HBV and HCV do not surpass 3/100,000 (with the exception of Finland), efforts to diminish alcohol consumption and stop the rises in obesity and diabetes would prevent a non-negligible number of liver cancers in addition to many other related morbidities.

Despite a comprehensive literature review, we were unable to identify HBV and HCV prevalence data in HCC cases for many countries in Eastern Europe, Central Asia, Oceania and Africa (Supporting Information, Fig. S1). The almost complete lack of data from Oceania, where limited data were available only for New Zealand, meant that we could not apply the model to extrapolate from countries with data to those without data in this region. Australia has a national hepatitis surveillance program that provides population prevalence data,\(^17\) and this has been used to estimate AFs for liver cancer in Australia of 16% for HBV and 19% HCV with a joint AF of 34%.\(^18\) The AF for HBV is comparable with our estimates for Europe and North America, but the AF for HCV is somewhat lower (Fig. 1).

Even when case series are available for HBV and HCV prevalence, there are still issues of generalizability. In some countries, case series originated from hospitals covering mainly urban areas (i.e., in France) or a small fraction of the country (i.e., in the Russian Federation). It is also possible that high-risk populations such as migrants originating from HBV-endemic areas or injecting drug users at high risk of HCV infection were under-represented in some HCC case series. A last caveat concerns international variations in the quality of HCC diagnosis: the typical precursor, cirrhosis, may lead to an early diagnosis in more developed countries or to death prior to the identification of HCC in less-developed countries. This report therefore underscores the need for better national and subnational cancer data to inform on the current public health impact of HCV and HBV epidemics. Statistical modeling is no substitute for collecting accurate data.

The aim of our statistical model is to be as parsimonious as possible, while accounting for the observed variation in the prevalence data. An important simplifying assumption in our model is that the relative risks for HBV and HCV infection are constant worldwide. The relative risk estimates come from a random-effects meta-analysis of 22 epidemiological studies of HCC that measured both HBV and HCV.\(^10\) The authors of this meta-analysis tested for heterogeneity in the relative risks of monoinfection. They reported \(p\) values of 0.81 for heterogeneity by time, 0.83 by study design and 0.026 by geographical area for HBV-only. The heterogeneity \(p\) values for HCV-only were 0.70, 0.33 and 0.022, respectively. The heterogeneity by area was largely driven by a single study of US army veterans (the only study from the US) in which 47% of cases had alcoholic cirrhosis\(^19\) and therefore alcohol was an important competing risk.

A second simplifying assumption is that our model does not include any national-level predictor variables, such as gross domestic product, prevalence of obesity or average alcohol consumption. The primary reason for not including these predictor variables is that they are general population statistics, whereas our outcome is prevalence in HCC cases. We do not think it is generally appropriate to mix these data from two different populations in the same model. Two potentially useful predictor variables are the estimated prevalence of HBV and HCV in the general population. For example, it is plausible that HBV prevalence in cases is higher in countries where HBV is endemic and this could be used to improve the extrapolations from our model. Nevertheless, we decided not to use this auxiliary information in our model. We wanted our estimates to be independent of and complementary to, previous estimates of the HBV and HCV burden. It is also important to consider the long latency of HCC when comparing prevalence of HBV and HCV in HCC cases versus the general population. As our estimates are based on prevalence in HCC cases, they reflect the causes of liver cancer present 20–40 years ago, whereas current prevalence of HBV and HCV in the general population is indicative of the future disease burden. This is of special importance for the evolution of HCV-related liver cancer as trends in HCV transmission in less developed countries and the universal implementation of anti-HCV treatment are not easily predictable.

In September 2015, the United Nations General Assembly adopted the 2030 Agenda for Sustainable Development, of which one important goal is to eliminate viral hepatitis as a public health threat by 2030.\(^20\) For HBV-attributable liver cancer, declines will certainly derive from the highly effective vaccination campaigns that have gained ground in less developed countries as the early 2000s. In 2015, WHO estimates that 84% of infants received at least 3 doses of hepatitis B vaccine, and 39% of newborns received the recommended birth dose.\(^21\) However, safe injection practices and blood donation control for HCV lag behind in some less developed countries,\(^21\) and HBV and HCV screen-and-treat interventions have not been implemented sufficiently anywhere. The success of treatments against HBV and HCV, will largely depend, as it has been seen for antiretroviral therapy, on the affordability of antiviral drugs, the simplification of treatment and monitoring protocols, and the capacity of individual countries to identify, reach and treat the vulnerable populations.
References

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer, 2013. (Accessed April 19, 2017 at http://globocan.iarc.fr/)

2. Shin HR, Oh JK, Masuyer E, et al. Comparison of incidence of intrahepatic and extrahepatic cholangiocarcinoma—focus on East and South-Eastern Asia. Asian Pacific J Cancer Prevent 2010;11:1159–66.

3. IARC. Biological agents. IARC Monogr Eval Carcinog Risks Hum 2012;100B:1–475. Accessed April 19, 2017 at http://monographs.iarc.fr/ENG/Monographs/vol100B/index.php)

4. Xia J, Jiang S-C, Peng H-J, et al. Association between liver fluke infection and hepatobiliary pathological changes: a systematic review and meta-analysis. PLoS One 2015;10:e0132673

5. Bosetti C, Turati F, La Vecchia C. Hepatocellular carcinoma epidemiology. Best Pract Res Clin Gastroenterol 2014;28:753–70.

6. Plummer M, de Martel C, Vignat J, et al. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Global Health 2016;4:e609e16.

7. de Martel C, Maucort-Boulch D, Plummer M, et al. Worldwide relative contribution of hepatobiliary carcinoma. Hepatology 2015;62:1190–200.

8. Blakely TA, Bates MN, Baker MG, et al. Hepatitis B carriage explains the excess rate of hepatocellular carcinoma for Maori, Pacific Island and Asian people compared to Europeans in New Zealand. Int J Epidemiol 1999;28:204–10.

9. Bruzzi P, Green SB, Byar DP, et al. Estimating the population attributable risk for multiple risk factors using case-control data. Am J Epidemiol 1985;122:904–14.

10. Cho LY, Yang JJ, Ko KP, et al. Coinfection of hepatitis B and C viruses and risk of hepatocellular carcinoma: systematic review and meta-analysis. Int J Cancer 2011;128:176–84.

11. Blet WJ, Day NE. Synergy and interaction: are they equivalent? Am J Epidemiol 1979;110:99–100.

12. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.

13. United Nations Development Programme. Human Development Report 2013. The Rise of the South: Human Progress in a Diverse World. New York, USA: United Nations Development Programme, 2013. (Accessed April 19, 2017 at http://hdr.undp.org/en/2013-report)

14. Ott JJ, Stevens GA, Blach S, et al. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol 2014;61:545–57.

15. Ott JJ, Stevens GA, Groeger J, et al. Global epidemiology of hepatitis B virus infection: new estimates of age-specific antibody to HCV seroprevalence and endemicity. Vaccine 2012;30:2212–9.

16. Mohd Hanafiah K, Groeger J, Flaxman AD, et al. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology 2013;57:1333–42.

17. The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2012 University of New South Wales, Sydney, NSW 2052: The Kirby Institute, 2012. (Accessed April 19, 2017 at https://kirby.unsw.edu.au/report/annual-surveillance-report-hiv-viral-hepatitis-sis-2012)

18. Antonsson A, Wilson LF, Kendall BJ, et al. Cancers in Australia in 2010 attributable to infectious agents. Austral N Z J Pub Health 2015;39:446–51.

19. El-Serag HB, Richardson PA, Everhart JE. The role of diabetes in hepatocellular carcinoma: a case-control study among United States Veterans. Am J Gastroenterol 2001;96:2462–7.

20. WHO. Global health sector strategy on viral hepatitis 2016–2021 Geneva, Switzerland: WHO Press, 2016. (Accessed April 19, 2017 at http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf?ua=1)

21. WHO. Global Hepatitis Report 2017 Geneva: World Health Organization, 2017. (Accessed April 19, 2017 at http://apps.who.int/iris/bitstream/10665/2558161/9789241565455-eng.pdf?ua=1)