

## Global burden of HBV-attributable liver cancer

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### Population Attributable Fraction

The population attributable fraction (AF) of a carcinogenic infectious agent is the proportion of cancer cases that would not have occurred if everyone in the population had either avoided infection or had been successfully treated before progression to cancer. IARC has estimated the global burden of cancer attributable to infections (Plummer et al, 2016) based on AF estimates for the 11 infectious agents classified as carcinogenic to humans (IARC, 2012).

The AF is often calculated using Levin's formula:

$$AF = \frac{p(R - 1)}{1 + p(R - 1)}$$

Where R is the relative risk and p is the prevalence in the population. IARC's work on AF for infections has used the alternative formula:

$$AF = p_c \left( \frac{R - 1}{R} \right)$$

where  $p_c$  is the prevalence in cases. There are two reasons for preferring the second formula. Firstly, it is generally easier to obtain a representative sample of cases than controls for the estimation of prevalence. This is particularly important when there are secular changes in prevalence so that population prevalence depends strongly on age. Secondly, the relative risks associated with carcinogenic infections are typically very large, in which case the AF is approximately equal to the prevalence in cases.

### Prevalence of HBV and HCV in hepatocellular carcinoma

We conducted a systematic literature review of cases series from 1989 to 2014 that reported joint seroprevalence of hepatitis B surface antigen (HBsAg) and antibodies against HCV (anti-HCV)<sup>1</sup> in at least 20 adult cases of hepatocellular carcinoma (HCC) (de Martel et al, 2015).

Overall 119,000 HCC cases were identified from 260 studies in 50 countries. Asian and African countries generally showed a predominance of HBV. Conversely, most European and American countries showed a preponderance of HCV over HBV and a substantial fraction of cases negative for both viral markers. No eligible studies were available in Oceania, large parts of Africa, Eastern Europe and Central Asia.

Twelve countries had sufficient survey data to show changes in prevalence before and after the year 2000. These results are shown in [Figure 1](#). The United States, Brazil and Germany showed evidence of increased prevalence of HCV. Conversely, Japan and Italy showed a decline in the proportion of HCV-positive HCC.

### Global burden of HCC attributable to hepatitis viruses.

The data from the systematic review were used to estimate the global burden of liver cancer attributable to HBV and HCV. The estimation proceeded in three steps: 1) extrapolation of prevalence estimates to countries without data; 2) calculation of country-specific AF by combining estimates of prevalence and relative risk; 3) combination of AF with estimates of cancer burden and aggregation to regional estimates of cancer attributable to HBV and HCV.

The extrapolation of geographically limited prevalence data (50 countries) to obtain global prevalence estimates was carried out using a generalized linear mixed model, with two levels of random effects: one level represented the variation of prevalence between studies conducted in the same country and the second level variation between countries in the same region. Eight geographical regions based on the United Nations classification and used by GLOBOCAN 2012 (Ferlay et al 2014) were used in the model, each with its own baseline prevalence. The model had three functions:

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<sup>1</sup> Studies using a first-generation enzyme-linked immunoabsorbant assay for HCV were excluded.

1. To provide prevalence estimates for countries with no data.
2. To improve estimates for countries with limited data by “borrowing strength” from prevalence data for other countries in the same region.
3. To quantify the uncertainty in the prevalence estimates for all countries so that appropriate confidence intervals could be calculated for the AF.

Relative risk estimates for HBV and HCV were obtained from a meta-analysis of 20 case-control studies and 2 cohort studies of HCC that tested all participants for both viruses (Cho et al, 2011). This gave a summary relative risk of 23.4 (95% CI: 17.2–31.7) for infection with HBV alone, and 27.6 (95%CI: 19.8–38.4) for infection with HCV alone. Coinfection with HBV and HCV yielded a summary relative risk of 51.1 (95%CI: 33.7–77.6), consistent with the additive excess relative risk model for interaction. The advantage of this model for attributable risk calculations is that the AFs for HBV and HCV are additive:

$$AF(HBV + HCV) = AF(HBV) + AF(HCV)$$

This is not the case in general for other interaction models (Blot and Day, 1979).

Country-specific AF estimates are shown in [Figure 2A](#) for HBV and [Figure 2B](#) for HCV. HBV is the dominant cause of liver cancer (i.e. AF > 50%) in large parts of Asia, Oceania and some parts of sub-Saharan Africa. Conversely few liver cancers in Northern America and in Western and Northern Europe are attributable to HBV (AF < 20%). HCV is globally less important as a cause of liver cancer, with less geographical aggregation of countries showing a high AF (notably, Mexico, Italy, Pakistan, Japan and North Africa). Less aggregation for HCV is explained by the predominant source of HCV transmission in the past, i.e., iatrogenic transmission that depends on the system of health delivery and can be different even among countries with similar developmental status.

Country-specific AF estimates were combined with estimates of the burden of liver cancer from Globocan 2012 (Ferlay et al 2012) and aggregated into regional and estimates. The results are shown in [Table 1](#). Overall 410,000 cases of liver cancers worldwide are attributable to HBV and 150,000 to HCV. This corresponds to an AF of 53% (95%CI 49-57) for HBV and 20% (95%CI 18-22) for HCC. There are large variations in AF between regions. The lowest AF for HBV is found in Northern Europe (AF=8%; 95%CI 2-17) and the highest in Eastern Asia (AF=64%, 95%CI 58-69). Aggregation of by human development index (United Nations Development Program, 2013) showed important differences by development status In less developed countries (low and very low HDI) HBV is responsible for two thirds of liver cancer cases (AF=62; 95%CI 57-67), whereas in more developed countries (medium and high HDI) it is responsible for only one in four cases (AF=25%; 22-28).

## Conclusions

HBV and HCV are responsible for 72% of liver cancer cases worldwide, with wide geographical variations in the attributable fraction. The calculation of attributable fractions from prevalence data in case series is, in principle, straightforward. However, our estimates have been limited by issues in the available prevalence data. Notably, sparse geographical coverage of the prevalence data required the use of a statistical model to extrapolate to areas without data. In addition, sex-stratified prevalence data were rarely reported. Therefore we report combined estimates of the liver cancer burden for men and women, despite important differences in the burden of liver cancer by sex.

It should also be noted that the attributable fraction is retrospective in nature, in the sense that it evaluates the public health importance of past causes of cancer that are currently causing cancer. The attributable fraction should not be confused with the proportion of future cancer cases that may be avoided by a specific public health intervention.

## References

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**Figure 1.** Changes in joint prevalence of HBV and HCV in cases of hepatocellular carcinoma before (light grey) and after (dark grey) the year 2000.

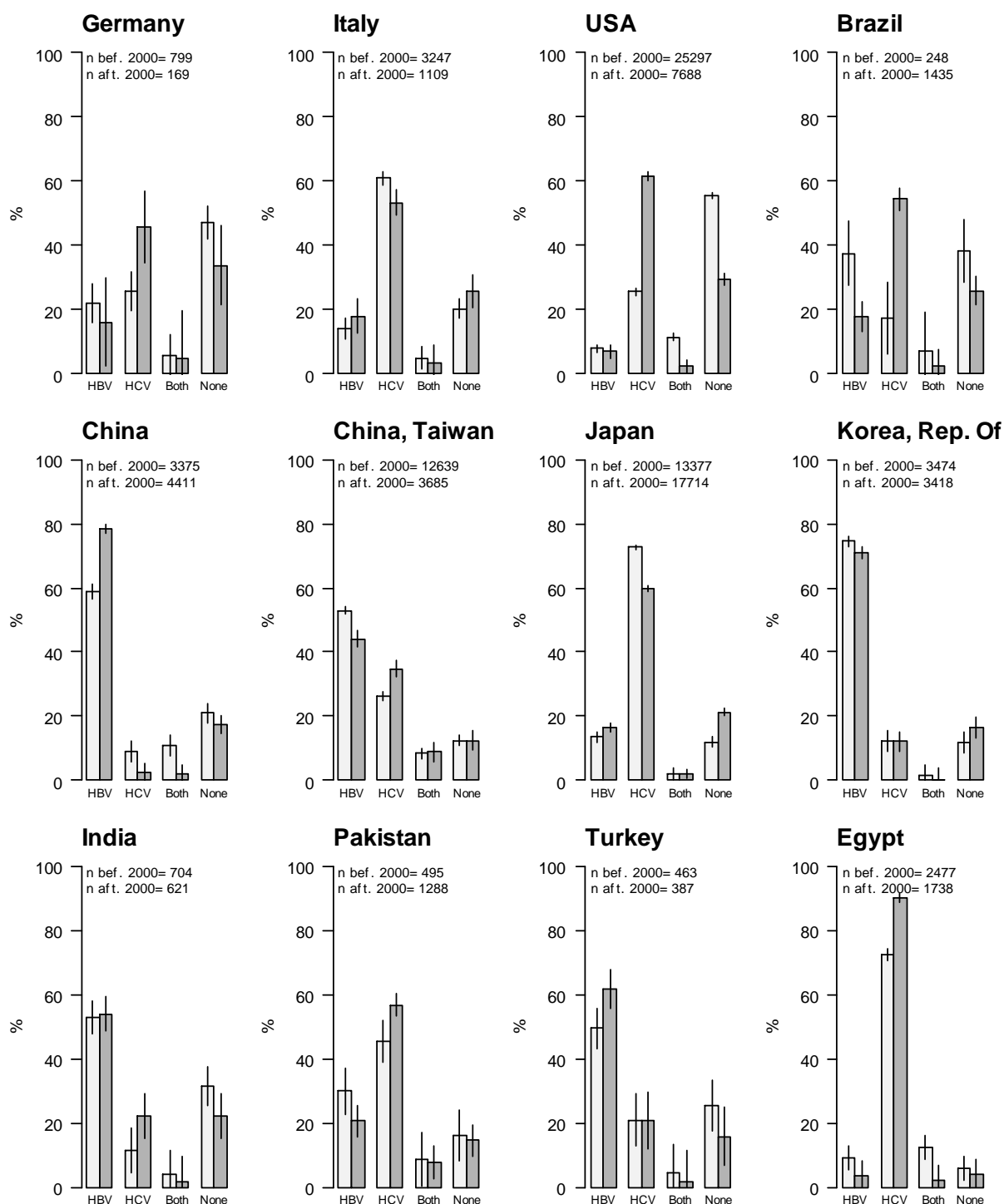


Figure 2A. Estimated fraction of liver cancer attributable to hepatitis B virus by country

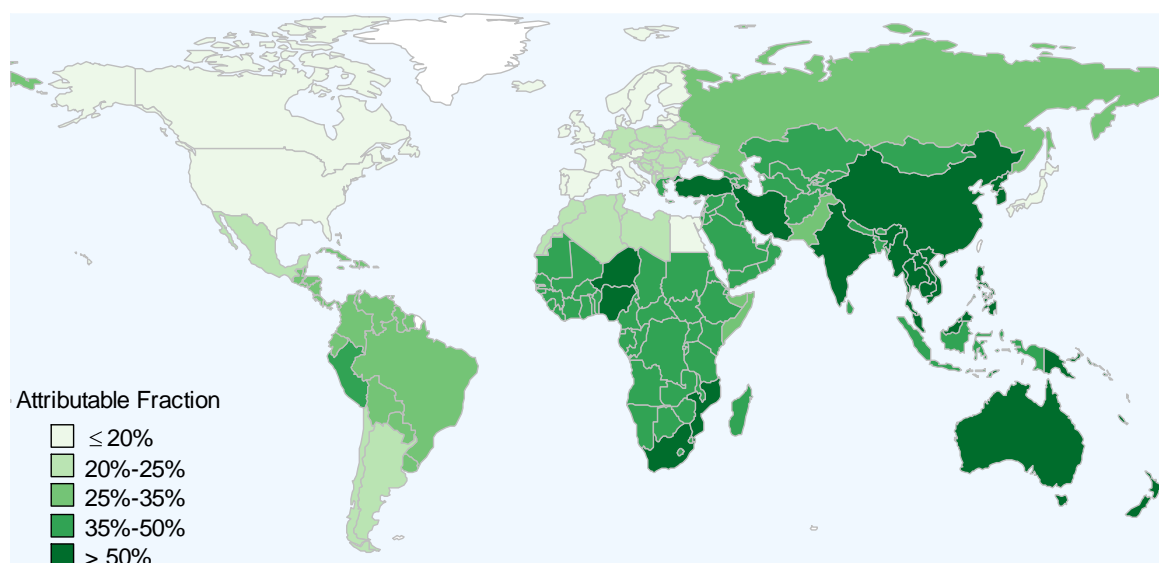
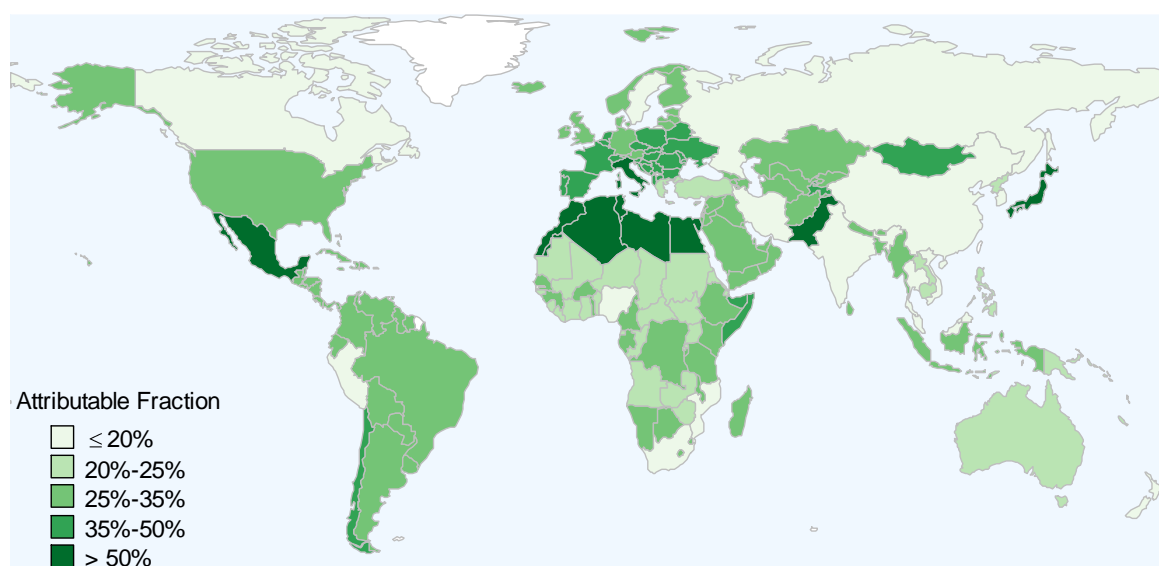


Figure 2B Estimated fraction of liver cancer attributable to hepatitis C virus by country



**Table 2.** Estimated number of liver cancer cases in 2012 attributable to HBV and HCV by geographical region and by development status

	Total cases N	Attributable cases					
		HBV			HCV		
		N	AF (%)	95 % CI	N	AF (%)	95 % CI
<b>By region</b>							
Northern Europe	6400	490	8	(2 – 17)	1800	28	(11 – 51)
Rest of Europe	57000	12000	21	(17 – 26)	22000	39	(31 – 46)
Northern America	33000	4100	12	(7 – 19)	11000	33	(22 – 45)
Latin America	30000	8400	28	(18 – 40)	11000	36	(24 – 49)
Eastern Asia	540000	340000	64	(58 – 69)	72000	14	(11 – 16)
Western-Central Asia	48000	23000	47	(39 – 56)	12000	24	(17 – 31)
Northern Africa	20000	2600	13	(8 – 20)	15000	75	(67 – 82)
Sub-Saharan Africa	39000	19000	50	(39 – 60)	8000	21	(13 – 30)
Ocenia	28000	980	50	(43 – 57)	390	20	(16 – 25)
<b>By development status</b>							
More developed	190000	47000	25	(22 – 28)	72000	38	(34 – 42)
Less developed	580000	360000	62	(57 – 67)	81000	14	(12 – 17)
<b>Total</b>	<b>770000</b>	<b>410000</b>	<b>53</b>	<b>(49 – 57)</b>	<b>150000</b>	<b>20</b>	<b>(18 – 22)</b>