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World-wide Relative Contribution of Hepatitis B and C Viruses in Hepatocellular Carcinoma

Catherine de Martel,[1] Delphine Maucort-Boulch,[1,2,3,4] Martyn Plummer,[1] and Silvia Franceschi[1]

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are major causes of hepatocellular carcinoma (HCC). In order to assess the relative contribution of HBV and HCV to HCC worldwide, and identify changes over time, we conducted a systematic review of case series published up to the year 2014. Eligible studies had to report seroprevalence of both hepatitis B surface antigen (HBsAg) and antibodies to HCV (anti-HCV), alone and in combination, for at least 20 adult HCC cases. Studies using a first-generation enzyme-linked immunosorbent assay test for HCV were excluded. A total of 119,000 HCC cases in 260 studies were included from 50 countries. Most European and American countries show a preponderance of HCV over HBV and a substantial fraction of viral marker–negative cases. Asian and African countries generally show a predominance of HBV. The fraction of HCV-positive HCC cases is substantial in Taiwan, Mongolia, Japan, and Pakistan as well as in Western-Central Asia and Northern Africa. No eligible studies were available in Oceania, large parts of Africa, Eastern Europe, and Central Asia. The United States, Brazil, and Germany show evidence of higher prevalence of HCV in HCC since the year 2000. Conversely, Japan and Italy show a decline in the proportion of HCV-positive HCC. *Conclusion*: HBV and HCV are predominant causes of HCC in virtually all world areas, with a growing fraction of HCC cases in several countries attributable to HCV. (HEPATOLOGY 2015;62:1190-1200)

Primary liver cancer ranks worldwide as the fifth-most common cancer in men and the ninth in women, with an estimated number of new cases occurring per year of 554,000 and 228,000 for men and women, respectively.[1] A rapidly evolving, highly fatal disease, primary liver cancer is the second-most common cause of death from cancer worldwide in both sexes; it is estimated to be responsible for 746,000 deaths per year (9% of the total deaths from cancer).[1] Chronic infections with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) are the strongest risk factors for hepatocellular carcinoma (HCC), the histological type of liver cancer that accounts for the vast majority of primary liver cancer. Other strong risk factors exist, such as alcohol, metabolic syndrome,[2] and heavy exposure to aflatoxin.[3] Though aflatoxin exposure, which mainly potentiates the carcinogenicity of HBV infection,[4] has been reduced by better grain storage and dietary changes in several developing countries, obesity and diabetes, which were mainly associated with HCC in HCV-infected populations, are increasing in both developed and developing countries.[5]

The contribution of individual risk factors, alone or in association, varies greatly by different geographical area and may change over time.[4,6-8] In well-identified HBV endemic areas, HBV is typically acquired at birth or in early childhood. Conversely, HCV infection can be acquired at any age through contaminated needles and blood, and HCV prevalence increases steadily with age owing to the accumulating risk of exposure. Because HCV transmission mainly depends on country-specific medical practices, notably safety of injections and blood transfusions, and the importance of transmission through intravenous drug use,[7] high-prevalence countries may be

Abbreviations: anti-HCV, antibodies to HCV; ELISA, enzyme-linked immunosorbent assay; GBD, Global Burden of Disease; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDI, Human Development Index; HIV, human immunodeficiency virus; UN, United Nations.

From the [1]International Agency for Research on Cancer, Lyon, France; [2]Service de Biostatistique, Hospices Civils de Lyon, Lyon, France; [3]CNRS UMR5558, Laboratoire de Biométrie et Biologie Evolutive, Equipe Biostatistique Santé, Pierre-Bénite, France; and [4]Faculté de Médecine Lyon Est, Université Claude-Bernard Lyon 1, Lyon, France.

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found in proximity to low-prevalence countries.[8] Contrary to HBV infection, for which chronic carriage is rare when HBV exposure occurs after adolescence, HCV has a high probability of becoming a chronic progressive infection when HCV exposure occurs at any age.[9]

Here, we present the results of a systematic review of the seroprevalence of HBV and HCV, alone or in combination, in published HCC case series in order to infer the relative contribution of the two viruses to HCC worldwide and, where possible, to determine changes in seroprevalence over time. The study adds to the existing literature on global patterns of HBV and HCV infection and provides estimates of the fraction of HCC attributable to HBV and HCV in the countries where prevalence data are available.

Materials and Methods

In 2007, our group published a systematic review combining 27,881 HCC cases from 90 studies published between January 1, 1989 and October 31, 2006.[10] For the present report, we extended and updated the initial MEDLINE search up to 30 September 2014, using various combinations of the following MeSH terms: "hepatocellular carcinoma"; "liver neoplasms"; "hepatitis B virus"; "hepatitis B antibodies"; "hepatitis B antigens"; "hepacivirus"; and "hepatitis C antibodies". Additional relevant studies were identified in the reference lists of selected articles. The following languages were considered: English, French, Italian, Spanish, Portuguese, and Chinese.

Only case series of patients with a diagnosis of HCC were considered in this review. Two of the authors (C.d.M. and D.M.B.) independently selected studies of confirmed HCC diagnosed in adults, when the case series was believed to be representative of the general population in the corresponding catchment area. Case series were not considered for inclusion if they were based on special populations, such as health care workers, human immunodeficiency virus (HIV)-infected people, groups of patients with a specific comorbidity, or liver transplant patients in less-developed countries. Discrepancies were resolved by consensus. Multinational studies were eligible for inclusion when country-specific estimates were reported. Each country was considered as a separate study, so that the number of studies reported is larger than the number of publications. Multinational studies that only gave overall summaries were also included in pooled regional estimates when all countries were from the same region.

Eligible studies had to report seroprevalence of both hepatitis B surface antigen (HBsAg) and antibodies against HCV (anti-HCV), alone and in combination, for at least 20 adult HCC cases. Studies using a first-generation enzyme-linked immunosorbent assay (ELISA) test for HCV were excluded. The more sensitive and specific second- and third-generation assays have been available since 1992 and 1994, respectively.[11] Therefore, when no information on the HCV serology test was provided, we retained studies published after the year 1996 and/or including cases tested after 1994. In cases of multiple publications of the same HCC series, the most informative article was retained.

In addition to viral markers, the data extracted from each study included: first author; journal of publication; publication year; study period; study country; study population; and case selection methods. When available, age distribution and generation of HCV serology tests used were also retrieved. Prevalence of markers by gender was very rarely available. Studies reporting on only one serological marker, or studies for which data on combined infection could not be easily inferred from the published data, were excluded. Data entry was systematically double checked. Study period was defined as the median year of recruitment period. For studies for which this information was not available (usually small studies), the study period was set to be 2 years before the publication year.

The cases in each study were classified into four groups: HBV-positive only (HBsAg positive but anti-HCV negative); HCV positive only (anti-HCV positive but HBsAg negative); coinfected (both HBsAg positive and anti-HCV positive); and nonviral (both markers negative). Prevalence estimates for these four groups were summarized by country and within eight United Nations (UN) geographical regions as used in GLOBOCAN.[1] For two publications on HCC in immigrants to the United States, the cases were attributed to the

Address reprint requests to: Catherine de Martel, M.D., Ph.D., International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon cedex 08, France. E-mail: deMartelC@iarc.fr; fax: +33 (0)4 72 73 83 45.

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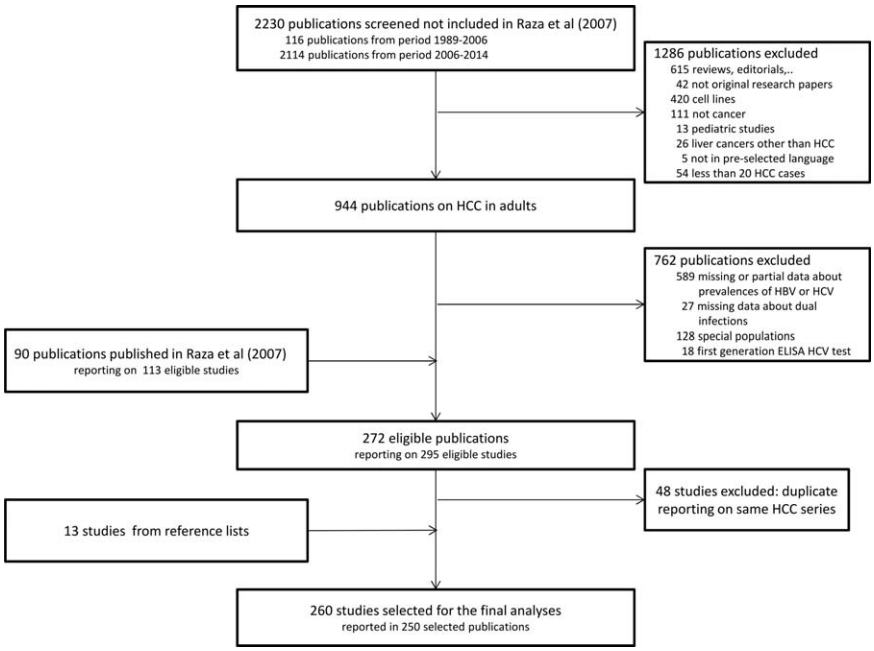

Fig. 1. Flow diagram of studies selected for inclusion in the systematic review.

country or region of origin.[12,13] Bar charts of the proportions of the four groups were drawn with their 95% confidence interval for each country showing more than 100 HCC cases overall. In order to report on the evolution of infection prevalence over time, studies were separated into two groups by study period: before the year 2000 and after the year 2000. This cutpoint was chosen because it was the median study period. Countries for which data were reported for more than 150 HCC cases in at least two studies for each of the two periods were additionally represented in double bar charts including 95% confidence intervals. Proportions of HCC cases positive for either viral marker were calculated by country, stratified by Human Development Index (HDI) classified into four groups as defined by the UN[14] (high, medium, low, and very low HDI), and graphically presented as a forest plot.

Mean age of HCC cases was calculated by country and region using data from studies that provided this information. Some studies also provided mean age among cases positive for a single viral marker (HBV positive only and HCV positive only) and these were also pooled by country and region. The pooled mean ages were calculated by weighted average, taking total cases positive for HBV or HCV infections as weights.

Results

Our searches in Medline identified 2,230 distinct publications not included in the previous review.[10] Of these, 944 were original publications reporting on at least 20 adult HCC cases. After excluding studies on special populations and those with inadequate viral marker data, 295 studies remained, including the 113 identified in the previous meta-analysis.[10] Thirteen additional studies were found in the reference lists of eligible articles. After removal of duplicate publications on the same case series, 260 studies remained, reported in 250 separate publications (Fig. 1; Supporting Table 1).

Overall, 119,006 HCC cases were identified in 50 individual countries and three multinational studies (Supporting Table 1). Study size varied substantially and so did the contribution of each country to the total number of cases. The majority of the cases were from Eastern Asia (39.2%), followed by North America (27.8%) and Europe (6.5%). No study was available from Oceania.

Table 1 shows the availability of studies reporting on age in the seven UN geographical regions, as well as for individual countries. Area- and country-specific mean age at HCC diagnosis, overall and by viral status from 29 informative studies, is also shown (coinfected cases excluded). HCC cases who were HCV positive only were generally diagnosed around 60 years of age in all regions (range, 59-65), whereas HBV-positive only cases were diagnosed earlier (range, 39-61). Age difference varied by region: It was 1-7 years in Europe and in the Americas, 6-11 years in Asia, and over 20 years in Africa, in which the mean age at diagnosis of HBV-positive HCC was over 10 years younger than in other regions.

Figures 2–4 show graphically the relative importance of viral markers of infection in HCC for countries with

Table 1. Age at Diagnosis in Cases Series of HCC Patients, Overall and by Hepatitis Virus Seromarker

	Studies Contributing to Overall Age		Studies Contributing to Age by Infection Type			
Country/Region	N Studies†	Mean Age*	N Studies	N Cases	Mean Age* at HBV-Positive HCC	Mean Age* at HCV-Positive HCC
Germany	7	61.2	3	408	55.9	62.8
Greece	2	63.9	1	333	62.2	66.1
Italy	8	63.6	1	204	60.2	65.2
Spain	4	62.7	1	94	44.2	63.0
Europe	**30**	**63.2**	**6**	**1,039**	**58.0**	**64.7**
USA	8	58.2	1	7,060	56.0	57.0
Northern America	**9**	**58.2**	**1**	**7,060**	**56.0**	**57.0**
Argentina	1	62.0	1	551	60.0	63.0
Latin America	**10**	**59.6**	**2**	**791**	**60.6**	**63.4**
China	24	51.7	1	413	51.2	63.2
China, Taiwan	16	58.2	3	8,894	53.2	65.1
Japan	23	65.2	6	4,414	57.0	68.2
Korea, Republic of	12	56.5	3	1,086	54.2	64.8
Mongolia	1	57.6	1	963	57.0	58.1
Thailand	2	53.8	1	101	49.5	52.7
Eastern Asia	**86**	**58.8**	**15**	**15,871**	**54.5**	**65.3**
Pakistan	10	55.7	1	201	49.7	56.3
Turkey	5	59.4	1	207	56.2	61.9
Western-Central Asia	**28**	**56.3**	**2**	**408**	**52.8**	**59.0**
Egypt	5	55.3	1	28	41.0	60.7
Northern Africa	**7**	**55.9**	**1**	**28**	**41.0**	**60.7**
Nigeria	3	52.0	1	64	46.7	64.8
Somalia	1	48.3	1	62	32.0	60.6
Sub-Saharan Africa	**15**	**46.3**	**2**	**126**	**38.9**	**62.6**

*Mean ages within country or region calculated by weighted average, taking total cases positive for HBV or HCV as weights.

†Bolded rows represent the mean age at diagnosis in seven UN geographical regions. Some countries contributed to overall age but not to age by infection type. Hence, figures do not add up to the total.

information on at least 100 cases. Detailed data for all countries are shown in Supporting Table 1. European and American countries are displayed in Fig. 2. With the exception of Russia and Greece, where HBV is dominant, European countries show a preponderance of HCV over HBV (HCV close to 60% of all HCC in Italy and Spain) and also a substantial fraction of marker-negative cases (from 21% in Italy to 82% in Sweden). The same preponderance of HCV is noted in most South American countries and in the United States, which shows a small fraction of HBV (8%).

Asian countries are displayed in Fig. 3. Eastern Asian countries generally show a large predominance of HBV infection, which is found in more than two thirds of cases in China, Hong Kong, Republic of Korea, and Vietnam and in more than 50% of cases in Malaysia and Thailand. In addition to high prevalence of HBV (around 50%), Mongolia and Taiwan also show a rather high prevalence of HCV (around 27%). With a high prevalence of coinfected cases (21%), Mongolia has the highest proportion of viral marker–positive HCC in the world, leaving only 2% of cases with no viral markers. Finally, Japan shows a unique profile in Asia, with a large predominance of HCV infection (65%), few HBV infections (15%), and very few coinfected cases (2%). In the Central Asia region, India and Pakistan show distinct viral profiles, with HBV being preponderant in India (53% HBV vs. 16% HCV) and HCV in Pakistan (54% HCV vs. 23% HBV), where the prevalence of coinfected cases is also non-negligible (8%). In Western Asia, the proportions of HBV and HCV are similar in Saudi Arabia and Yemen, whereas HBV infection is preponderant in Turkey.

African countries are displayed in Fig. 4. HBV is dominant in Sub-Saharan Africa. Egypt has the highest proportion of HCV in the world (80% HCV only and 8% coinfected with HBV).

Figure 5 illustrates the change in the relative importance of the four viral marker groups over two periods of time for 12 selected countries with sufficient data. Although nonviral HCC was predominant before 2000 in Germany, Brazil, and the United States, a significant increase in the proportion of HCV-positive HCC was observed in the period after 2000 (e.g., in the United States, the proportion of HCV increased from 25% in the first period to 60% in the second period). The proportion of HCV-positive HCC has also grown in Taiwan and in two HCV high-risk countries, Egypt and Pakistan, where the proportion of HCV-positive cases reaches 90% and 58%, respectively, in the latest period.

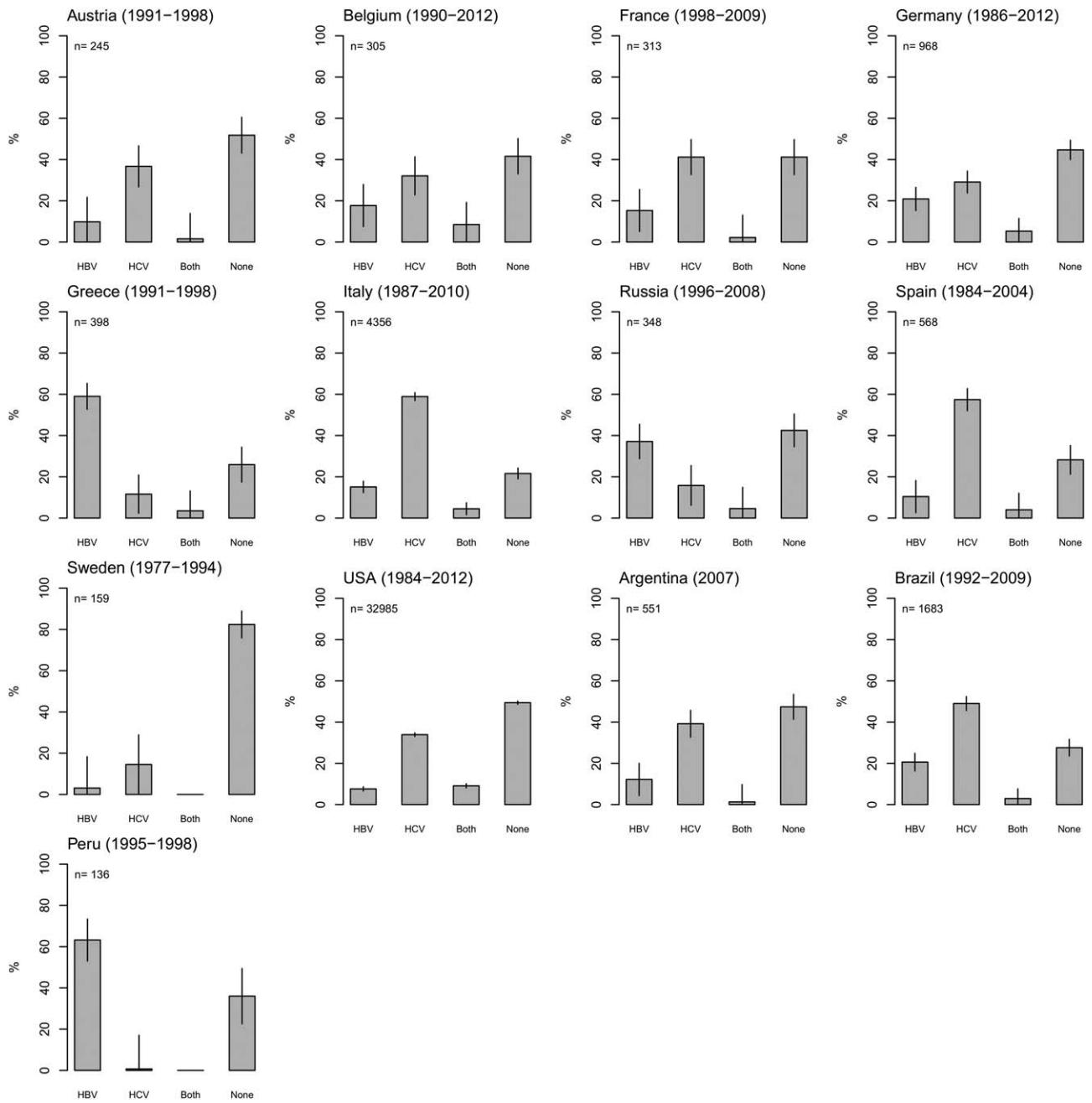

Fig. 2. Seroprevalence of HBsAg, antiHCV-Ab, both, and neither in patients with HCC in Europe and the Americas for countries with at least 100 HCC cases.

Conversely, Japan and, to a lesser extent, Italy show a decline in the proportion of HCV-positive HCC. Korea, India, and Turkey do not show statistically significant changes in either HBV or HCV between the two periods, although the proportion of HCV-positive HCC seems to be increasing in India. In China, the proportion of HBV-positive HCC has significantly increased, whereas the proportion of coinfected cases has decreased. Sufficient data were available for the United States and Japan to allow a further breakdown of the study period into three groups: before 2001, 2001-2005, and after 2005. The results, shown in Supporting Fig. 1, suggest that increases in the fraction of HCC attributable to HCV in the United States mainly occurred after 2005, whereas decreases in that fraction in Japan had already occurred before 2001.

Figure 6 shows the fraction of HCC positive for HBV and/or HCV for the 50 countries grouped in four categories according to their HDI.[15] The combined prevalence of HBV and HCV is over 60% in most countries. Only seven countries have an upper confidence limit below 60% prevalence (Sweden, Canada, United

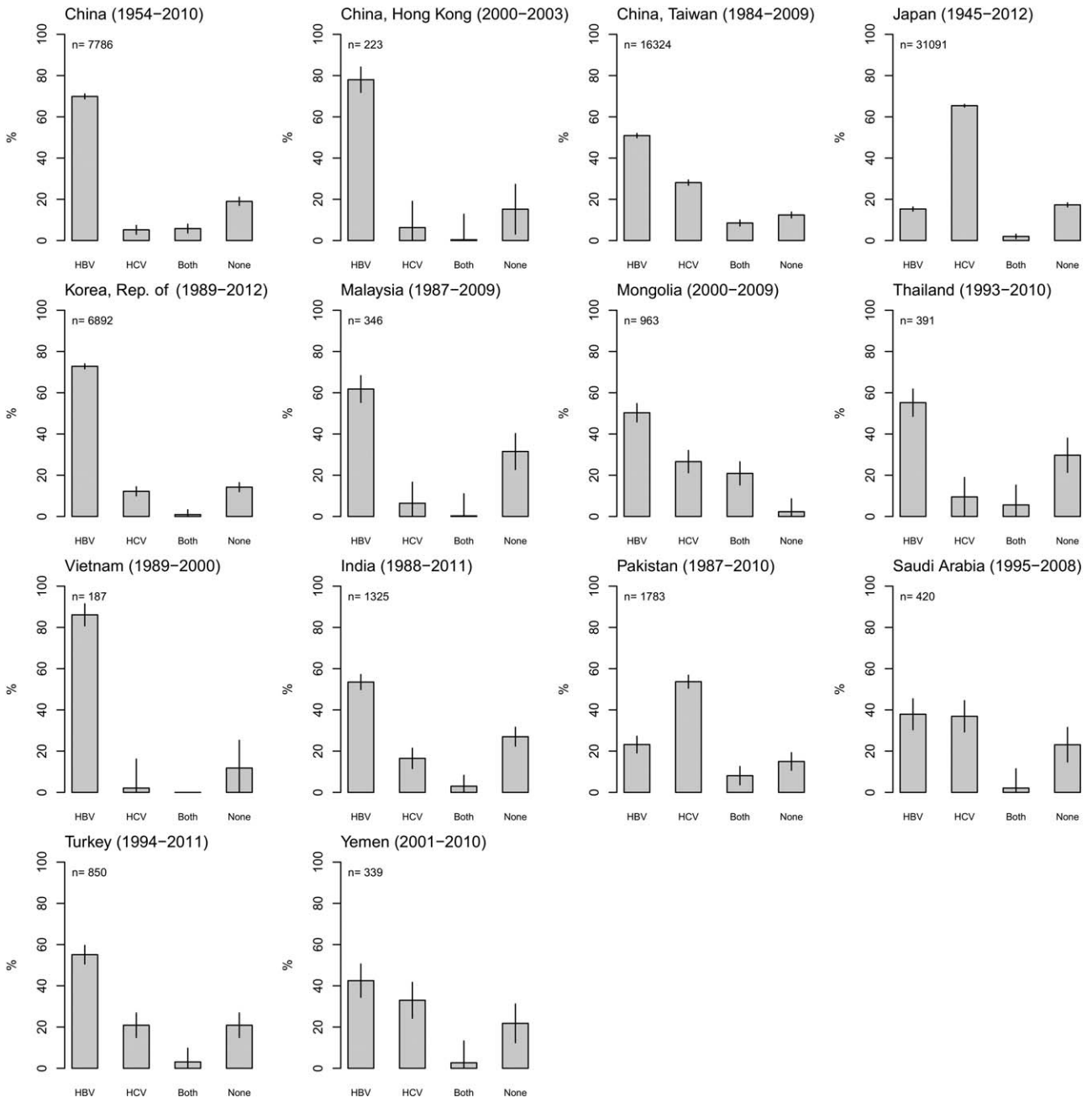

Fig. 3. Seroprevalence of HBsAg, antiHCV-Ab, both, and neither in patients with HCC in Eastern Asia and Western and Central Asia for countries with at least 100 HCC cases.

Kingdom, Austria, United States, Argentina, and Germany), and these are all in the high HDI group. However, the high HDI group is not homogeneous and also includes countries with high HBV and HCV prevalence similar to countries in the medium, low, and very low HDI categories.

Discussion

Our review shows a picture of the relative burden of HCV and HBV in HCC cases in 50 countries worldwide. If we assume that HCC cases positive for HBsAg or anti-HCV antibodies are caused by HBV and HCV respectively, then at least 60% of HCC are attributable to either HBV or HCV in most countries, particularly those with a medium or lower HDI classification. However, the relative contribution of HBV and HCV to HCC varies substantially by country.

The amount of data presented here represents a large increase, compared to our previous systematic review. We added 90,000 cases for a total of 120,000 worldwide. Among 12 new countries, four contributed more

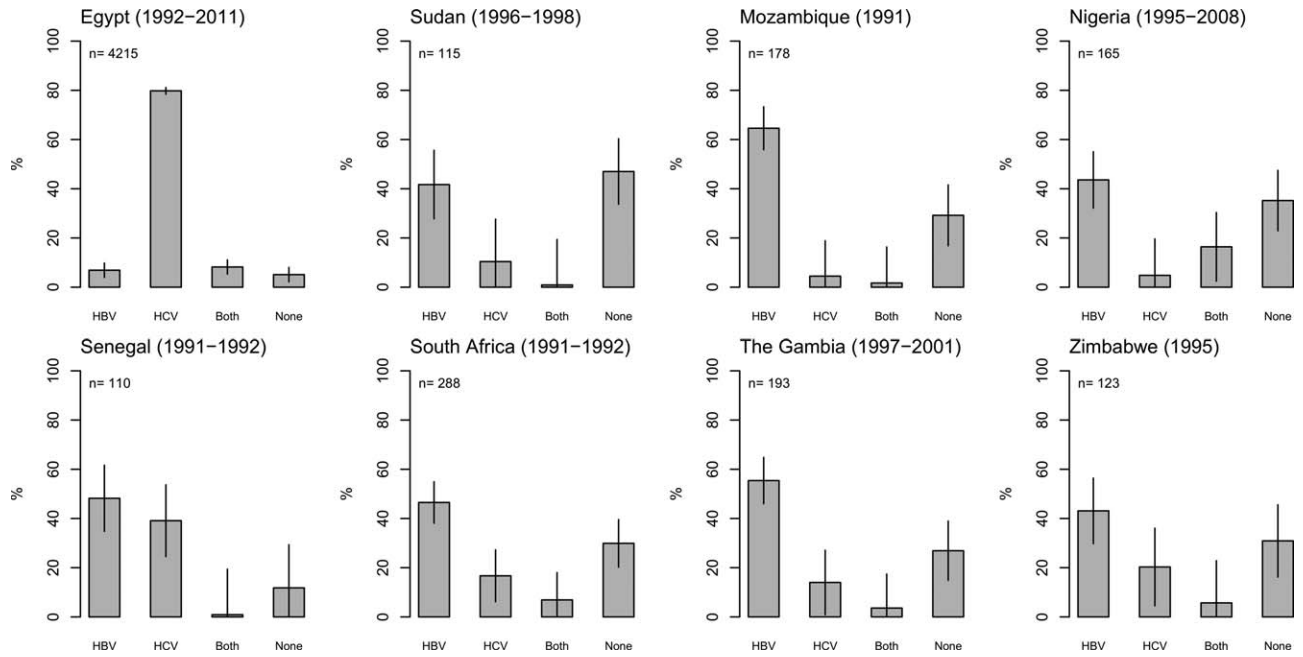

Fig. 4. Seroprevalence of HBsAg, antiHCV-Ab, both, and neither in patients with HCC in Northern Africa and Sub-Saharan Africa for countries with at least 100 HCC cases.

than 300 cases (Russia, Argentina, Malaysia, and Yemen). With the exception of Russia and Greece, where HBV is dominant, most European and American countries show a preponderance of HCV over HBV and a substantial fraction of viral marker–negative cases. Asian and African countries generally show a predominance of HBV infection, but the fraction of HCV-positive HCC is also substantial in Taiwan, Mongolia, and the Middle East and preponderant in Japan, Pakistan, and Northern Africa.

The large amount of data also allowed us to explore changes in HBV and HCV seroprevalence in HCC cases before and after 2000 for 12 countries. The proportion of HCV-positive HCC significantly increased in Germany, the United States, Brazil, Taiwan, Egypt, and Pakistan, whereas it decreased in Italy and Japan, the two countries that had been earliest hit by HCV epidemics. These observations confirm and expand previous reports on favorable or unfavorable trends in HCV-positive HCC for the same countries.[2,16-18] Conversely, the increase in the proportion of HBV-positive HCC and the concomitant decrease in HCV-positive or -coinfected cases in China was less expected. Improvements in transfusion practices were indeed implemented in China in the mid-1990s,[19] notably decreases in paid plasma and blood donors who were associated with massive transmission of blood-borne infections, including HCV and HIV, in the 1980s.[20] However, the information on the two periods derives from partially different Chinese provinces, notably an earlier over-representation of high HCV prevalence areas (e.g., Liaoning Province).[19] Hence, the relative increase in HBV-positive HCC may reflect either recent improvements in HCV control or problems of comparability between the two examined periods.

Data on the mean age at HCC diagnosis by viral status, available for 29 studies, show that the HBV-positive HCC cases are consistently younger than HCV-positive cases, but the age difference between the two groups varies by world area. The age gap is largest and the mean age at HBV-positive HCC diagnosis is youngest in Africa and some countries of Eastern Asia. These are areas in which HBV infection was transmitted vertically or in childhood, whereas the transmission of HCV infection through contaminated needles and blood transfusions is a more recent phenomenon that affects HCC risk at older age. In the United States, HCV-positive HCC and the less-frequent HBV-positive HCC are diagnosed at similar ages, probably on account of the predominance of intravenous drug users and persons born during 1945-1965 among chronic HCV carriers.[17]

Our review is mainly based on consecutive HCC cases diagnosed in a given hospital. On account of the severity of the disease, most cases are likely to seek medical care at some point and, therefore hospital-based series are likely to be representative of HCC cases in the general population. We chose to exclude studies known to have used a first-generation assay for anti-HCV antibodies, which was poor in both sensitivity and specificity.[21] All articles that did not specify the laboratory method for the anti-HCV test were published after 2009 and so were unlikely to have used a

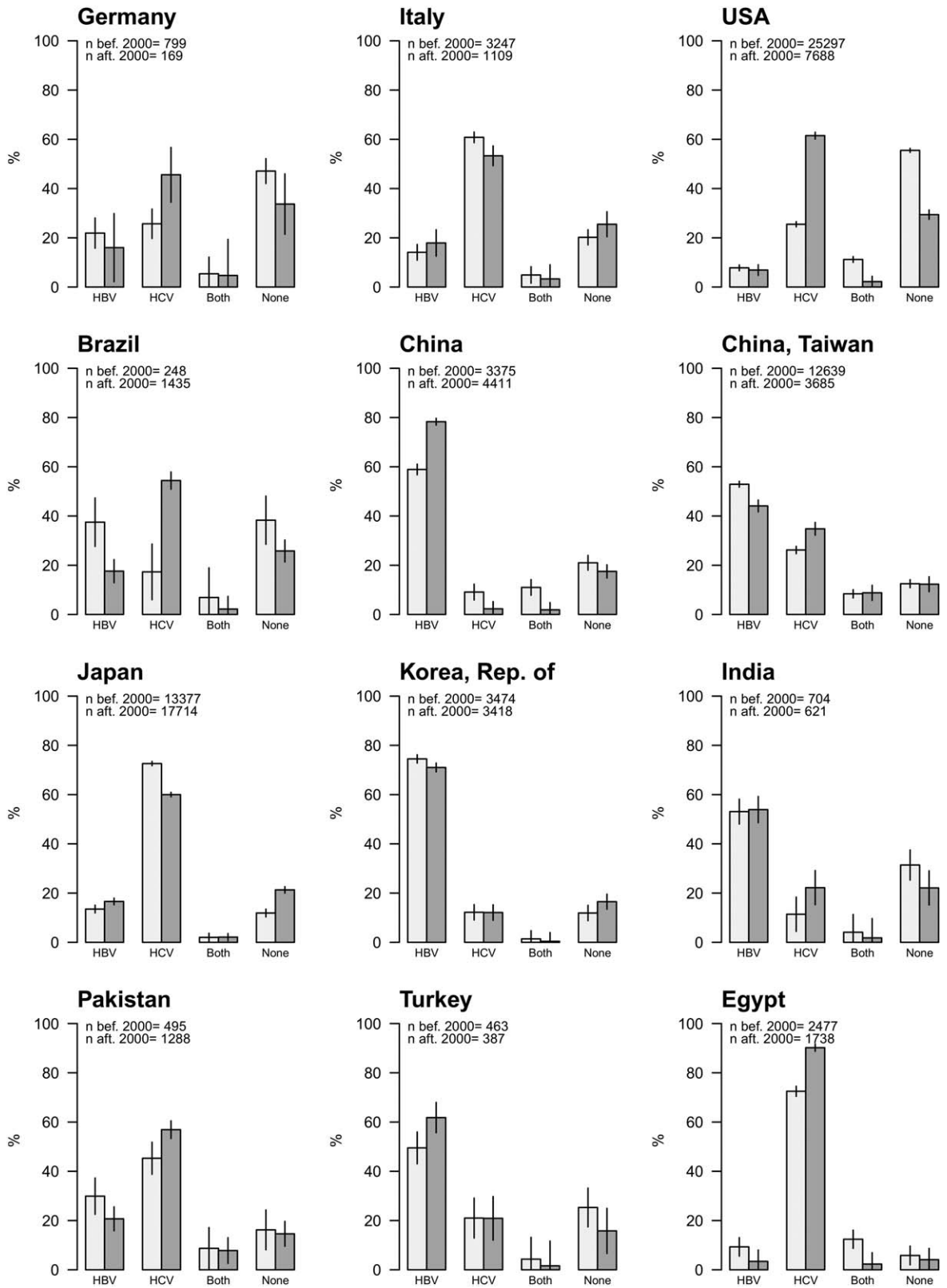

Fig. 5. Seroprevalence of HBsAg, antiHCV-Ab, both, and neither in patients with HCC in countries for which at least 2 studies, and at least 150 cases, are available in each period before (light gray) and after the year 2000 (dark gray).

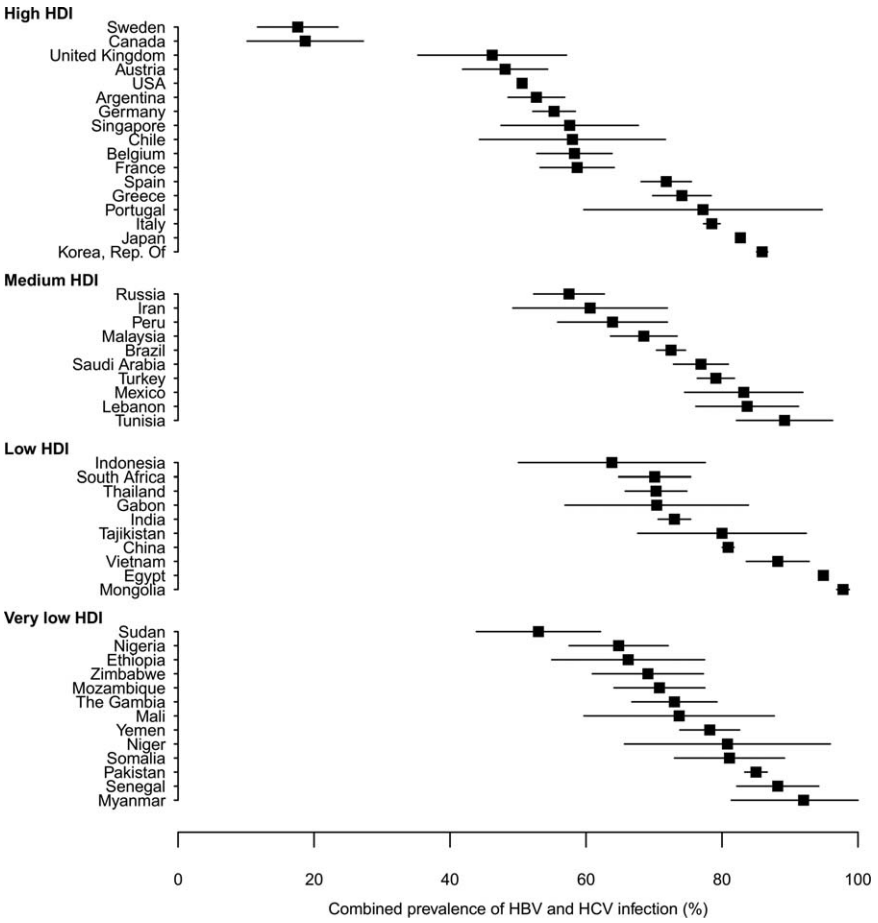

Fig. 6. Proportion of HCC cases positive for any hepatitis virus seromarker (HBsAg, antiHCV-Ab, or both) by country grouped by human development index (HDI).

first-generation assay. We included second-generation assays because the main advantage of the third-generation assay is increased sensitivity in newly infected individuals.[11] This should not be an issue in HCC patients who have presumably been infected for many years. The anti-HCV antibody assay has the limitation of being a marker of exposure, not chronic infection. Approximately 75%-85% of HCV-infected individuals develop chronic infection. We expect the proportion of anti-HCV positive HCC cases who are chronic HCV carriers to be higher, given that the cancer itself is evidence that the infection is chronic. Unfortunately, information on HCV RNA, which confirms the presence of an active infection, was very rarely available in the articles included in this review.

A high proportion of HBV- and/or HCV-positive HCC is found in countries, such as China, Republic of Korea, Mongolia, Pakistan, and Egypt, that show the highest HCC incidence rates worldwide.[1] However, the time gap owing to the long latent period between infection and HCC development should be borne in mind; for example, the proportion of HCV-positive HCC is still increasing in some high HDI countries in which the spread of HCV infection has been declining for decades[22] or is not yet evident in countries, such as Nigeria, that currently have high HCV prevalence in the general population.[8]

The main limitation of our present meta-analysis is the absence or scarcity of high-quality information for many countries. For example, the case series available from Oceania used a first-generation test for HCV and did not meet our inclusion criteria,[23] nor did a more recent linkage study that showed similar proportions of HBV and HCV infection in Australian HCC cases,[24] but did not include marker-negative HCC cases. In addition, the contribution of HBV infection may have been underestimated in some hyperendemic areas, notably China, because of HCC cases associated with occult HBV.[25-27] Our systematic review combines data from multiple sources. The impact of heterogeneity of diagnostic criteria and laboratory methods is difficult to quantify. Finally, we regret the lack of sex-specific information (HBV, but not HCV, is known to be more common in men than women) and other correlates of HCC risk (e.g., alcohol and tobacco consumption, as well as aflatoxin exposure).[2] Notwithstanding these limitations, our systematic review has the important strength of allowing the joint evaluation of the two most important causes of HCC.

A number of previous studies have reported global, regional, and country-level prevalence estimates of HBV and HCV infections in the general population. One systematic review has been recently published on the population prevalence of HBV[28] and two on HCV.[8,29] All three reviews show the same large variations between countries as found in the current study. Another study of HBV and HCV population prevalence in Europe[30] shows a low viral prevalence in North Western Europe in contrast with intermediate to high prevalence in Southern and South Eastern European countries, consistent with our findings in HCC cases.

An assessment of the relative contribution of HBV, HCV, alcohol, and other factors to liver cirrhosis mortality has recently been published as part of the Global Burden of Disease (GBD) project.[31] These estimates were derived from prevalence in cases of liver cirrhosis rather than the general population. Their findings on the relative contribution of HBV versus HCV are similar to ours: HBV predominates in Sub-Saharan Africa and Central and Eastern Asia, and HCV predominates in Europe and in the Americas. In contrast, the fraction of cirrhosis mortality attributable to nonviral causes is generally larger than our estimates of HCC with no viral markers. This difference is consistent with a lower risk of developing HCC in patients with alcoholic cirrhosis, compared to patients with viral cirrhosis.[32] Similarly, HCC is unusual in patients with other causes of cirrhosis, such as Wilson's disease or primary biliary cirrhosis.[33]

The GBD project has also published global estimates of mortality from all causes, including liver cancer[5] with country-specific estimates in an extensive online appendix (table 31, pp. 672-4110). Notably, for China, we estimate that 11% of HCC cases are HCV positive (including coinfections with HBV), whereas the GBD estimates that 37% of liver cancer deaths are the result of HCV. Conversely 76% of HCC cases in China are HBV positive (including coinfections), whereas the GBD estimates that 45% of liver cancer deaths are the result of HBV. These differences may be explained by the predominant use by the GBD of extensive modeling of HBV and HCV seroprevalence from general populations rather than from fatal HCC cases. Estimates of nonviral causes are similar in our present study and in the GBD project findings (19% vs. 17%).

In conclusion, we confirm the predominance of HBV and HCV in the etiology of HCC in virtually all world areas and highlight the growing fraction of HCC cases attributable to HCV infection in several countries. Improvements in the efficacy of treatments of HBV[34] and HCV infection[35,36] encourage great hopes for HCC prevention in chronic carriers of the two infections, but limited access and high cost of mass viral screening and new drugs are major challenges for secondary prevention. Therefore, we should reiterate the need for primary prevention of viral infections, notably universal vaccination against HBV, safe injections and blood transfusion practices, and avoidance of parenteral treatment when oral alternatives are available.

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Author names in bold designate shared co-first authorship.

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