



Mini-review

Epidemiology and prevention of hepatocellular carcinoma

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ABSTRACT

A meta-analysis on the seroprevalence of hepatitis B surface antigen (HBsAg) and antibodies against hepatitis C virus (anti-HCV) in 27 881 hepatocellular carcinomas from 90 studies confirmed wide international variations. A predominance of HBsAg was found in hepatocellular carcinomas from most Asian, African and Latin American countries, but anti-HCV predominated in Europe, North America, Japan, Pakistan, Mongolia, and Egypt. Anti-HCV was found more often than HBsAg in Europe and the United States. Twenty-five years after having been licensed, HBV vaccination programmes are now carried out in 158 countries, but they have yet to reach many high-risk populations in sub-Saharan Africa and Asia. In the absence of a vaccine, the prevention of HCV infection requires an integrated strategy (i.e., screening of blood donations, safe injection practices, and avoidance of unnecessary injections).

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1. Introduction

Hepatocellular carcinoma (HCC) represents approximately 6% of all new cancer cases diagnosed worldwide, with more than half of these occurring in China alone [1]. Relatively high incidence rates are also found in South Eastern Asia and in sub-Saharan Africa [1]. As it is one of the least curable malignancies, HCC is the third most frequent cause of cancer death among men worldwide [1].

Chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most important causes of HCC [2]. According to the World Health Organisation (WHO), approximately 350 million people are chronically infected with HBV [3], and 170 million with HCV [4] worldwide. There are no comparable statistics for the number of individuals coinfecting with HBV and HCV.

The relative importance of HBV and HCV infections in HCC aetiology is known to vary greatly from one part of the world to another [5], and can change over time [6]. In order to elucidate prevention priorities in different parts

of the world, we will examine in the present paper: (1) relative predominance of HBV and HCV infection in HCC in different continents and (2) progress made in the prevention of HBV and HCV infection.

2. Materials and methods

We have recently collated all published data on the prevalence of chronic HBV and HCV infection among HCC cases worldwide. Methods have already been reported [7]. Briefly, all studies which showed the prevalence of both hepatitis B surface antigen (HBsAg) and antibodies against HCV (anti-HCV), alone and in combination, for at least 20 HCC cases, were included. After exclusion of studies using first-generation ELISA for anti-HCV testing, 90 studies with relevant data on the prevalence of HBsAg and anti-HCV, covering 27 881 HCC cases from 36 countries, were available. The majority of cases were from Asia (66%) followed by the Americas (15%), Europe (12%) and Africa (7%).

We have also reviewed the state of implementation of vaccination against HBV and the obstacles to the prevention of HCV infection in different parts of the world.

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3. Results

3.1. Predominance of HBV or HCV in different continents

Substantial variations in HBsAg and anti-HCV prevalence in HCC cases were observed between countries and continents (Fig. 1).

In Asia, the largest number of HCC cases from any single country came from Taiwan, with 8595 cases identified from a single multi-centre study [6], followed by Japan and China [8]. The proportion of HBsAg⁺ HCC cases was greater than 50% in China, Taiwan, Korea, Thailand, Vietnam, and Turkey. The lowest proportion of HBsAg⁺ HCC cases was reported in Japan where there was a strong predominance of anti-HCV seropositivity in HCC cases (68%) [9]. A higher proportion of anti-HCV⁺ than HBsAg⁺ HCC cases was also found in Pakistan (45%), and in Mongolia (40%), where HBV/HCV coinfection was also very frequent (25%). In China, anti-HCV was found twice as often in combination with HBsAg than alone. The highest proportion of HCC cases seronegative for both hepatitis viruses was found in India (37%) [7].

The countries in Europe where the largest numbers of HCC cases were studied were Italy [10,11], Greece [12] and Germany [13]. The proportion of HBsAg⁺ HCC cases (56%) was higher than that of anti-HCV⁺ HCC in Greece, whereas the opposite was observed everywhere else in Europe. In Italy and Spain, the proportions of anti-HCV⁺ HCC cases were 43% and 48%, respectively. Seropositivity for anti-HCV was significantly higher than for HBsAg also in Austria and Sweden, whereas in Germany the seroprevalence of the two viruses was similar. HBV/HCV coinfection was rare in most European studies, whereas HCC cases seronegative for both hepatitis viruses were relatively common (e.g., over 80% in Sweden).

A majority of American studies on HCC and hepatitis viruses were conducted in the United States, with two-thirds of HCC cases coming from a nation-wide linkage study for the Surveillance Epidemiology and End-Results Program [14]. In the United States, 9% of the HCC cases were HBsAg⁺ and 22% were anti-HCV⁺. The prevalence of HBV/HCV coinfection in HCC cases was 3.2% and a high proportion (67%) of HCC cases were seronegative for markers of both hepatitis viruses. In Brazil, 37% and 18% of HCC cases were HBsAg⁺ and anti-HCV⁺, respectively. Only 207 additional HCC cases were available from other American countries (Peru and Mexico), where prevalence of HBsAg exceeded that of anti-HCV.

Nearly half of the data on HCC in Africa came from Egypt [15], where a very high proportion (69%) of HCC cases was anti-HCV⁺. All other African countries showed a preponderance of HBsAg seropositivity. HBV/HCV coinfection was below 10% anywhere in Africa, whereas approximately 30% of HCC cases were seronegative for both hepatitis viruses in South Africa and Mozambique.

3.2. Prevention of HBV infection

HBV vaccines were first licensed in the United States in 1981. Formerly, they were plasma-derived and composed of purified HBsAg [16]. Nowadays, HBV vaccines are predominantly produced by recombinant DNA technology. The vaccine is administered in a 3 dose series and has resulted in high immunogenicity and efficacy, which has so far been monitored using relatively short-term measures (i.e., reduction in acute HBV infection and serial seroprevalence studies in vaccinated populations) [16].

Despite declines in anti-HBsAg titres to relatively low-levels, immunocompetent immunised individuals have not developed chronic hepatitis infection in 10- to 22-year follow up [17]. HBV vaccine within 12–24 h after birth, followed by a 3-dose vaccine series, has been shown to be effective in preventing vertical transmission which is very common in Asia [16]. The safety of the vaccine has been demonstrated in large studies [16]. Concerns were expressed about the possibility of the vaccine having caused some cases of multiple sclerosis, diabetes mellitus and demyelinating diseases, but an expert panel dismissed the presence of a causal association between the vaccine and these conditions [18]. Break-through infections by HBV mutant escapes among successfully vaccinated persons have also been excluded [16].

Declines in incidence and mortality rates from HCC have been reported already in children and adolescents in Taiwan, which established the first HBV immunisation programme in 1984 [19]. A better estimate of the decrease in the HCC burden achieved by HBV vaccination will be possible in approximately a decade in the two large randomised trials of HBV started in 1986 in the Gambia [17] and in 1990 in Qidong, China [20], both formerly highly endemic areas for HBV.

In 1992, the WHO recommended the integration of the HBV vaccine into national immunisation campaigns. As shown in Fig. 2 (www.who.int/immunization_monitoring), the number of countries that introduced the vaccine and implemented global infant coverage grew steadily from 17 in 1989 to 96 in 2000, mainly due to substantial increase of funds from international organisations such as the Global Alliance for Vaccines and Immunisations (GAVI). By 2005, 158 of the 192 WHO Member States had infant HBV vaccination programmes in place. Over half (62%) of these countries reported $\geq 80\%$ coverage by their programmes. The 34 countries that did not introduce infant HBV vaccination notably include several highly endemic countries in sub-Saharan Africa. Several developed countries with low HBV endemicity, including the United Kingdom, Scandinavian countries and Japan, do not routinely vaccinate children, but have instead chosen to target high-risk groups (e.g., immigrants from high HBV endemicity areas, adolescents, and adults with risk factors for HBV infection).

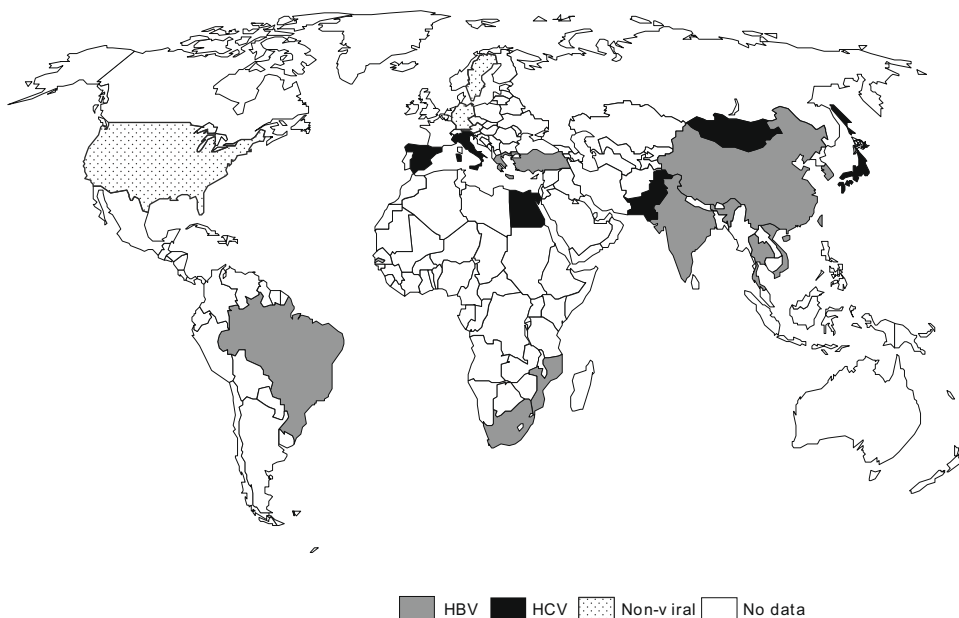


Fig. 1. Predominant causes of hepatocellular carcinoma (hepatitis B virus, hepatitis C virus, and seronegative for both) by country.

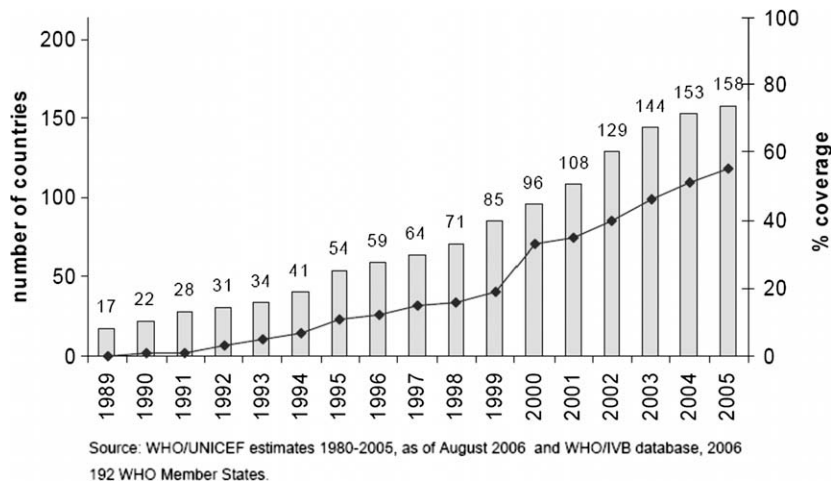


Fig. 2. Number of countries that introduced hepatitis B virus (HBV) vaccine in children and global infant HBV vaccine coverage, 1989–2005 (www.who.int/immunization_monitoring).

Priorities for the future are clearly to expand the number of high-endemicity countries that include HBV vaccination in infant immunisation schedules and to improve coverage in countries that have already opted to do so. The drop in the price of the HBV vaccine and the achievement of vaccine donating organisations should help to make these targets possible. Policies of selective immunisation of high-risk individuals have been seldom effective and, therefore, routine HBV vaccination is now also advocated in low-endemicity countries on the grounds that whenever a potentially devastating disease like HCC is easily preventable, steps should be taken to achieve this outcome.

3.3. Prevention of HCV infection

Research into new prophylactic and therapeutic vaccines is also ongoing for HCV. However, HCV has in common with other RNA viruses some characteristics that have greatly undermined past efforts to produce efficacious vaccines: (1) they display high genetic and antigenic diversity and mutate very rapidly in the host; (2) they induce, after natural infection, strong humoral and cellular responses that seem, however, unable to eliminate the infection or prevent reinfection; and (3) no small animal model or cell culture systems were available until recently to help vaccine developments.

Several candidate vaccines (e.g., virus-like particle vaccines) against HCV have long been tested in chimpanzees [21], and induced a strong cellular-immune response. Vaccination did not prevent the chimpanzees from becoming infected, but the course of the infection was apparently attenuated.

HCV infection is reaching worrying levels in many developing countries and the problem does not seem to have received sufficient attention as yet. In the absence of a vaccine against HCV, its prevention is more challenging than the prevention of HBV and requires an integrated strategy involving screening of blood donations, safe injection practices, and systematic avoidance of unnecessary injections. The misperception that many treatments that can be given orally are “better” if injected is unfortunately still widespread among patients and health workers in low-resource countries [22], and represents an obstacle to attempts to slow the spread of any blood-borne infection, including HIV.

4. Discussion

Our recent meta-analysis, based on nearly 30000 HCC cases, confirms wide international variation in the relative importance of HBV and HCV in this disease [7]. As expected, HBV infection was found substantially more often

than HCV infection in HCC cases from the majority of Asian and African countries with the available data. Conversely, more HCC cases were found to be anti-HCV⁺ than HBsAg⁺ in Europe and in the United States, as was also the case in Japan, Pakistan, Mongolia and Egypt.

More than half of HCC cases were both HBsAg⁻ and anti-HCV⁻ in the United States and some North European countries, thus pointing to the relative importance of heavy alcohol consumption [23] and, possibly, obesity and diabetes mellitus [24] in areas where hepatitis virus prevalence and HCC incidence are low.

Unfortunately, we did not find any information on HBV and HCV infection among HCC cases in Eastern Europe, Russia, Central Asia and the majority of African and Latin American countries. None of the studies we found from Oceania using second- or third-generation ELISA met our inclusion criteria. However, a record-linkage study from New South Wales, Australia showed a similar proportion of HBsAg⁺ (45%) and anti-HCV⁺ (53%) HCCs and low frequency of HBV/HCV coinfection (2%) among 281 virus-related HCC cases [25].

In addition to lack of data from many parts of the world, some weaknesses of meta-analyses of HCC like ours should be borne in mind. Important secular trends may be concealed as suggested by the largest study we identified [6], which showed a steady increase in the proportion of HCC cases related to HCV in the last two decades in Taiwan. The vast majority of studies did not provide information on occult HBV infection. Occult HBV infection seems, however, to have little or no clinical significance, at least among immunocompetent individuals [26]. Most importantly, owing to the long latent period of HCC, seropositivity among HCC cases does not reflect the current importance of the two viruses in the relevant population but rather that two or three decades earlier.

Based upon prevalence of the infections in different world populations and a relative risk of 20 for both viruses, Parkin [5] estimated the fraction of HCC attributable to HBV and HCV in 2002 to be 23% and 20% in developed

countries, respectively, and 59% and 33% in developing countries. Our simpler approach, based on HCC cases only, was mainly dictated by the wish to use information from many world populations for whom information on HCC was available but no data on population prevalences of HBV and HCV existed. Our meta-analysis suggests, however, that the relative contribution of HCV to the current HCC burden in middle-aged and old individuals in developed countries and in some developing countries might be higher than in Parkin [5]. In fact, seroprevalence surveys on which attributable risks are based tend to over-sample young individuals at low risk of HCV infection (e.g., blood donors and pregnant women) [27,28].

In conclusion, our findings underline the importance of strengthening HBV vaccination campaigns but also the urgency to upgrade the prevention of HCV infection in the list of priorities in many developing countries. In the absence of a vaccine, HCV prevention requires an integrated strategy including screening of blood donations, safe injection practices and avoidance of unnecessary injections [22].

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