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The epidemiology of hepatocellular cancer: from the perspectives of public health problem to tumor biology

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The epidemiology of hepatocellular cancer (HCC) can be viewed from several important perspectives. The conventional perspective includes the overall public health impact of HCC, which is increasing in incidence in many regions of the world. The epidemiology of HCC can also be viewed from the perspective of variation in underlying disease associations such as viral hepatitis or the recently recognized link to nonalcoholic fatty liver disease (NAFLD). Of perhaps increasing importance with recent advances in therapy of HCC, the epidemiology of HCC can also be viewed from the perspective of variation in HCC biology. This lesser known perspective may depend in part on the underlying liver disease and the cell origin of the cancer, whether of hepatocyte or stem cell origin. This aspect is likely to become central to diagnosis and management of HCC with the further development of targeted therapeutics. The relative efficacy of these agents will likely depend on the biochemical pathways active in a given hepatocellular malignancy. This, in turn, is likely to be related to the epidemiological associations of HCC.

Key words: hepatocellular cancer, viral hepatitis, NASH, NAFLD, cirrhosis

The epidemiology of hepatocellular cancer (HCC) can be viewed from several important perspectives: first, the conventional aspect of overall public health impact of HCC; second, variation in underlying disease associations such as viral hepatitis or the recently recognized link to fatty liver; and third, epidemiological variation in HCC biology. Emerging biological agents may eventually be shown to work better or worse depending on the biochemical pathways active in a given hepatocellular malignancy, the biology of which is likely to be related to its epidemiology. Here, we review the epidemiology of HCC from these perspectives: (1) overall public health impact, (2) underlying etiology of liver disease, and (3) epidemiological aspects of cancer biology.

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Public health perspective

By annual incidence, hepatocellular cancer (HCC) is the fifth most common cancer worldwide and the third leading cause of cancer death, although there has long been noted wide geographic variation such that certain regions in Asia and Africa have 40-fold-more cases based on the age-adjusted incidence rate than other regions of the world.[1,2,3] From cancer registries, it is estimated that there were 564 000 new cases of HCC in the year 2000, accounting for 7.5% of cancer in men and 3.5% of cancer in women worldwide.[4] Among the common threads emerging from these studies are that men are twice as commonly afflicted as women and that viral hepatitis plays a role in the majority of cases. The reason for the male preponderance has raised questions about a possible hormonal link, but more recent experimental data and the lack of efficacy of hormonal manipulation suggest that other factors, perhaps related to sex-based inflammatory response, are also involved.[5,6,7] However, of greatest importance from the public health perspective, the incidence of HCC has been rising worldwide, with particularly steep increases documented in many industrialized countries including Japan, the United States, and Denmark.[8,9]

In Japan, age-adjusted death rates attributed to primary liver cancer began to increase in 1975 from 10 000 annually to approximately 35 000 in the year 2000. This sharp increase is largely attributable to hepatitis C, although rising rates of obesity may also be contributing (see below), while hepatitis B has contin-

ued to play an important but relatively stable or slightly diminishing role. In the United States, this sharp increase in incidence, also attributable in large part to hepatitis C and nonalcoholic fatty liver disease (NAFLD), over the past 25 years has been associated with an increasing HCC-associated mortality from 1.54 to 2.58 per 100 000 between 1980 and 1990.[10,11] In the United States, substantial variation has been noted among different ethnic groups with the highest rates among Asians, Hispanics, and African Americans compared with Euro-Americans but with a characteristic increased risk in all groups with increasing age.[12,13] Consistent with these overall epidemiological trends, we have seen a remarkable increase in annual cases of HCC over the past 5 years, such that a separate and weekly HCC tumor board was established several years ago to more effectively triage the patients among the various disciplines involved in their care. Although previously unusual in the United States because there were few cases, similar programs are increasingly common now to better handle the worsening problem.

From the public health perspective, the role of environmental and exogenous toxins also warrants consideration. A number of such factors have been implicated in the development of HCC.[14] Aflatoxin, a potent hepatocarcinogenic mycotoxin, is perhaps the best characterized of these. Exposures result from ingestion of contaminated grains, noted especially in Africa and parts of Asia. Recent work shows that the mechanism may involve silencing of glutathione S-transferase because of its promoter hypermethylation, which was observed in 46% of HCC in one study and correlated to levels of aflatoxin-DNA adducts, in contrast to other potential environmental toxins such as aromatic hydrocarbons that showed no significant relationship.[15] Aflatoxin may also play a role in a few HCC in Western countries.[16] Although it is difficult to separate from alcohol-related cirrhosis, alcohol itself appears to act synergistically to increase the risk of HCC in other conditions such as chronic viral hepatitis, and this risk appears to be significantly magnified by simultaneous tobacco exposure.[17,18] Chronic arsenic exposure from drinking has also been implicated as a risk for HCC, although the evidence appears less convincing.[19] Other environmental toxins could play an indirect role through induction of chronic liver injury, such as a nonmetabolic syndrome-associated form of nonalcoholic steatohepatitis (NASH) that has been reported among petrochemical workers.[20]

The link to viral hepatitis

Bosch et al. have estimated that viral hepatitis plays a role in up to 80% of all HCC, with roughly two-thirds related to HBV and one-third to HCV.[4] To a large extent, the greater impact of HBV reflects populations in which vertical transmission is common, resulting in a high prevalence of endemic HBV, early age exposure, and subsequently an increased incidence of HCC. Indeed, a recent case-control study from India confirmed the previously well-described impact of hepatitis B (Table 1).[21] In this study, any positive marker for hepatitis B (with or without surface antigen and in the presence or absence of cirrhosis) increased the risk of HCC, with an overall odds ratio (OR) of 48 [95% confidence interval (CI) = 25–92]. In comparison, the OR for polymerase chain reaction (PCR)-positive hepatitis C *with* cirrhosis was 5 (95% CI = 2–15). In another study, both hepatitis B viral load and genotype appeared to influence the risk of HCC, especially in men over 30 years of age, where a higher risk of HCC was observed with genotype C and higher viral levels.[22] Inflammatory activity also appears to influence the outcome of

Table 1. Comparison of viral risk factors and ETOH for hepatocellular carcinoma (HCC)

Condition	Odds ratio	Confidence interval
Hepatitis B		
Any marker positive	48.02	25.06–91.98
HBsAg positive	38.98	19.55–77.71
Anti-Be or anti-Bc alone	12.34	2.84–53.61
Hepatitis C		
Anti-HCV positive, PCR positive	5.45	2.02–14.71
Heavy ETOH alone	2.83	1.51–5.28

A case-control study of 213 patients with HCC and 254 non-disease controls. Significant synergy was also noted between HCV and ETOH but only if cirrhosis was also present. In contrast, the presence of any HBV marker positive in this study revealed substantial risk even in the absence of cirrhosis

HBsAg, hepatitis B surface antigen; anti-Be, antihepatitis B E antigen; anti-Bc, antihepatitis B core antigen; anti-HCV, antibody to hepatitis C; PCR, polymerase chain reaction for hepatitis C viral RNA; ETOH, ethanol-related liver disease

Source: Adapted from Kumar et al.[21]

HCC in chronic HBV, thus indicating control of viral replication as part of the therapeutic regimen.[23] HBV DNA has also been detected in some HCC in the absence of serological markers, indicating that HBV may contribute to HCC risk even in the absence of overt infection.[24]

Although hepatitis B remains a significant contributor to HCC worldwide and especially in regions of Asia with high rates of endemic infection, such as China and Korea,[25] the recent explosive increase in HCC in Western countries and Japan is more likely attributable to actively replicating HCV and associated cirrhosis. In an extended natural history study, Fattovich et al. demonstrated that 1%–4% of patients with HCV-related cirrhosis will develop HCC per year.[26] Moreover, as pointed out by Seeff in a recent summary statement on the impact of HCC, the time course and natural history of the recent worldwide HCV epidemic indicates that the worst is yet to come.[27] Indeed, given the high prevalence of HCV and the fact that 20%–30% of infected patients will develop cirrhosis, it is likely that the peak incidence of HCC related to this disease can be expected in the next 5–15 years, barring any major new breakthroughs in therapy. The increasing prevalence of NAFLD, which may act independently in the development of HCC or synergistically, especially with hepatitis C, is further discussed next.

The link to cirrhosis

Cirrhosis is present in about 80%–90% of HCC patients and constitutes the largest single risk factor.[28] Its presence impacts survival, strongly influences treatment decisions, and clearly necessitates the increasingly common multidisciplinary approach to HCC management.[29] The risk of developing HCC among cirrhosis patients varies with the underlying disease and regionally among disease subsets (Fig. 1). The highest estimated 5-year cumulative risk is seen with HCV cirrhosis (30% in Japan versus 17% in the West), followed by hemochromatosis (21%), HBV cirrhosis (15% in Asia and 10% in the West), alcoholic cirrhosis (8%), and biliary cirrhosis (4%).[30] As discussed next, the type of underlying liver disease influences aspects of tumor biology such as cell origin, which in turn may influence response to emerging forms of therapy with biological modifiers.

Details of the mechanisms of carcinogenesis involved in these different forms of cirrhosis are beyond the scope of this article. However, it is worth noting here that changes in fat metabolism, including expression of adipocyte-like gene pathways, appear to play a role in both hepatic regeneration and sometimes in neoplastic transformation.[31,32] This relationship to fat metabolism

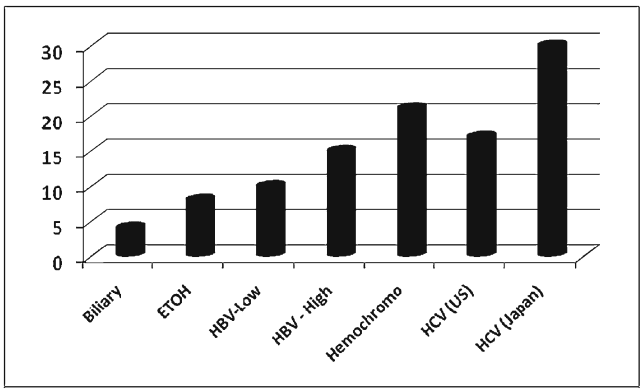

Fig. 1. Estimated 5-year cumulative risk (%) in cirrhosis patients based on underlying cause of liver disease. *Biliary*, biliary cirrhosis; *ETOH*, ethanol-related cirrhosis; *HBV-Low*, hepatitis B from regions with low rates of endemic infection; *HBV-High*, hepatitis B from regions with high rates of endemic infection; *Hemochroma*, hemochromatosis; *HCV (US)*, hepatitis C-related cirrhosis in the United States; *HCV (Japan)*, hepatitis C-related cirrhosis in Japan. (Adapted from Fattovich et al.[26])

appears to be important both in NAFLD-related cancer and in HCV, where steatosis, steatohepatitis, and associated oxidative stress are increasingly recognized as significant risks or cofactors in HCC development (see following). Other factors that are superimposed on cirrhosis and significantly influence the risk for HCC include older age, male sex, concomitant alcohol use, and, in some regions, aflatoxin exposure, as mentioned earlier.

The emerging link to NAFLD

Obesity constitutes a significant risk of cancer mortality in general and an increasingly recognized risk factor for hepatocellular cancer in particular.[33,34,35,36] Longitudinal case studies indicate that this epidemiological association derives largely from obesity-associated steatosis and secondary liver injury related to NASH, a condition that can lead to cirrhosis and HCC alone, or it may act synergistically with other disorders such as hepatitis C. Although ethnic variation exists, about 90% of people with obesity [body mass index (BMI) >30 in Western countries] have fatty liver, ranging from simple steatosis to more severe forms of NASH, including cirrhosis.[37] Additional epidemiological data indicate a significantly increased risk of hepatocellular carcinoma among diabetic patients.[38,39,40] Thus, HCC shares in common the two major risk factors found in NAFLD: obesity and diabetes.[41,42,43] As noted earlier, this relationship likely reflects the effects of NAFLD and NASH.

NAFLD and NASH are well-recognized disorders in many Western countries, and now these problems are

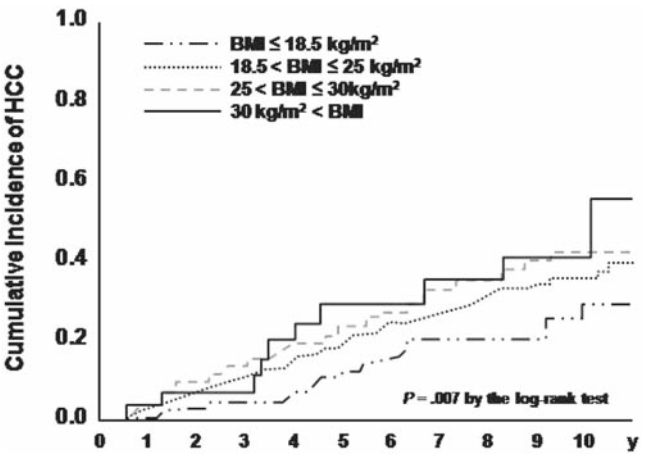

Fig. 2. Risk of hepatocellular carcinoma (HCC) by body mass index (BMI) in chronic hepatitis C cirrhosis. As discussed in the text, the increased risk with higher BMI most likely represents the combined effects of steatosis and chronic hepatitis C, particularly on stem cell proliferation in the liver. (Adapted from Ohki et al.[53])

also emerging in many Asian regions, including Japan and Korea.[44,45] A number of detailed case studies (including several from Japan and recently summarized by Bugianesi[46]) have documented the development of HCC in NASH usually, but not invariably, associated with antecedent progression to cirrhosis. Indeed, in some of these case studies, the development of HCC is noted only after progression of NASH to the late stage of cryptogenic cirrhosis.[47] This association is also supported by epidemiological data. In one series of 105 consecutive HCC patients, 51% had underlying cirrhosis caused by hepatitis C and 29% had cryptogenic cirrhosis, among which 50% had either histological or epidemiological factors to suggest antecedent NASH.[48] Thus, at a minimum NAFLD alone appears to account for 13% of HCC in Western series. A similar relationship between cryptogenic cirrhosis, NASH, and HCC appears to be emerging in some regions of Asia as well.[49]

However, this prevalence figure probably greatly underestimates the relative contribution of NAFLD to carcinogenesis, as steatosis appears to act synergistically with other conditions to promote HCC development. This relationship is best seen in chronic hepatitis C cirrhosis with coexisting features of metabolic syndrome such as obesity and associated steatosis (Fig. 2).[50,51,52,53] Another recent study from Yamaguchi, Japan revealed that steatosis is also an independent predictor of postoperative HCC recurrence in HCV-associated HCC [relative risk (RR) = 3.31; CI = 1.49–7.41; $P = 0.003$].[54] Among patients with grade 2 steatosis in this series, the 5-year recurrence was 100%, versus 60% in those with grade 0.

The mechanisms of carcinogenesis in NAFLD remain to be resolved, but the pathophysiological components of this disorder, especially when steatohepatitis is present, include lipid peroxidation, oval cell proliferation, and increased growth factors [such as insulin and transforming growth factor (TGF)]. These conditions essentially recapitulate the three essential components of carcinogenesis: (1) *initiation*—oxidative stress and lipid peroxidation; (2) *promotion*—with oval cell proliferation; and (3) *progression*—resulting from to oxidation-induced mutations and elevated trophic factors such as insulin and TGF.[55,56,57,58,59,60] In addition, the hepatic progenitor cell (HPC or oval cell) constitutes a suspected cell of origin for up to 50% of HCC (see following, under Epidemiology of HCC biology) and undergoes proliferation in both experimental and human NASH.[61,62] The degree of proliferation parallels several parameters of histological injury in NAFLD and also correlates to steatosis in hepatitis C.[60,63] These circumstances can be likened to "the perfect storm" for carcinogenesis in chronic cirrhotic HCV and steatosis, with proliferation of cells in the setting of oxidative stress and increased trophic factors associated with the metabolic syndrome such as hyperinsulinemia.

Epidemiology of HCC biology

There is much phenotypic and genotypic variation within HCC, some of which is predictable by epidemiological associations. For example, chromosome 8q gains and MYC overexpression in human HCC have been demonstrated to exist significantly more often in HCC related to ETOH and HCV than in cryptogenic (and presumably NASH-related) HCC.[64] With the recent emergence of new therapeutic biologicals such as the multi-kinase inhibitor sorafenib, the importance of understanding the epidemiological aspects of HCC biology is taking on greater importance. It is likely that tumor biology will influence the response or nonresponse to various interventions. Thus, genetic and associated phenotypic variations in HCC are likely to emerge as important decision points in determining optimal therapy.[65]

It is estimated that about 28%–50% of HCC carry markers (anti-CK 19) for origin in the hepatic stem cells.[66] Moreover, this variety appears to behave differently (more aggressively) after surgical intervention.[67] Based on proliferative patterns noted in NASH and HCV with steatosis, it seems likely that HCC from these cells will be more common in these disorders, although we are not aware of work demonstrating this conjecture. Other genetic factors have been grouped into proposed classification systems. For example, Chiang et al. recently proposed a classification system for HCV-

Table 2. Proposed molecular classification of HCC and clinical correlations

Class	Name	Estimated %	Association
1	Beta catenin mutated	26%	Larger lesions
2	Proliferation group	25%	Vascular invasion
3	Interferon response group	16%	Better prognosis
4	Chromosome 7 polysomy	10%	Recurrence
5	No distinction	—	—

A proposed molecular classification of hepatocellular cancer and clinical correlates based on integrative genomic analysis in 103 HCC with HCV-related chronic liver disease based on work by Chiang et al. presented at European Association for the Study of Liver Disease (EASL) 2008
The epidemiological associations of this and other working classifications remains to be fully defined
Source: Adapted from Chiang et al.[68]

derived HCC that appears to have important clinical correlations (Table 2).[68]

In addition to tumor-specific variables, the epidemiology of host genetic factors, which are also likely to influence HCC behavior, is also an area of active investigation. For instance, epidermal growth factor (EGF) polymorphisms have recently been linked to the risk of developing HCC in patients with cirrhosis.[69] All these associations are likely to have important epidemiological and possibly clinical correlations, much of which remains to be defined. However, it is important to begin to think of HCC epidemiology not only in conventional terms, but also in molecular and genetic terms, which may provide important clues to facilitate early detection in certain populations and the likely efficacy of newer anticancer therapy.

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