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REVIEW

Changing Epidemiology of HCC: How to Screen and Identify Patients at Risk?

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Abstract

The prognosis of patients with hepatocellular carcinoma is dependent on the stage of tumor at diagnosis. The earlier the tumor is found, the higher the chances to offer a curative treatment. In order to diagnose hepatocellular carcinoma early, patients at risk should be enrolled in a surveillance program. The population at risk is usually defined as patients with cirrhosis. These patients should have twice a year a ultrasonographic examination of the liver. However, more and more patients will develop hepatocellular carcinoma in the context of nonalcoholic fatty liver disease which is tightly linked to obesity and diabetes. In these patients, this approach is jeopardized by the difficulty to perform a sonography of good quality due to the obesity and more importantly by the fact that hepatocellular carcinoma occurs frequently in the context of nonalcoholic fatty liver disease before the cirrhosis. This article reviews the impact of the changing epidemiology of hepatocellular carcinoma on its screening.

Keywords Hepatocellular carcinoma · Liver cancer · Surveillance · Population at risk · Epidemiology

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Key Messages

- Primary prevention through immunization and secondary prevention through antiviral treatment will severely alter the epidemiology of HCC in the next decades.
- NAFLD constitutes an emerging major risk factor for HCC and will contribute substantially to the global burden of HCC.
- While the overall risk of HCC is low, a significant proportion of HCCs in the context of NAFLD develops without cirrhosis.
- The presence of cirrhosis in the context of NAFLD warrants systematic HCC surveillance.
- The long-term HCC risk of patients who were successfully treated for hepatitis C and of patients under NUC treatment for hepatitis B has yet to be defined.
- Lifestyles such as smoking, obesity, and diabetes, and gene polymorphism such as PNPLA3 rs738409 C>G might be used to stratify patients at risk for HCC and to identify those who might profit from surveillance.

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Introduction

Hepatocellular carcinoma (HCC) contributes significantly to the global burden of disease and mortality. Primary liver cancer ranked seventh among cancer-incidences worldwide and was the fourth leading cause of cancer-related mortality in 2016 [1]. Among primary liver cancer, HCC is the most common histological subtype and accounts for approximately 75% of cases [2].

The burden of liver cancer varies considerably by geographic region and sex due to the distribution of underlying diseases, genetic factors as well as varying exposure to environmental and behavioral risk factors. Globally, hepatitis B virus (HBV) is the leading cause of liver cancer death, accounting for 33% of liver cancer deaths, followed by alcohol and hepatitis C virus (HCV) infection [3]. While these communicable diseases and modifiable risk factors are targeted by new treatment regimens and preventive strategies, other risk factors are emerging [4]. Therefore, the pattern of global HCC occurrence is shifting.

The prognosis of primary liver cancer is poor, showing a five-year relative survival rate of 18.1% (95% CI 17.3–18.9%) for cases diagnosed with liver cancer from 2006 to 2012, seconded only by the low survival rate of pancreatic cancer [5]. As treatment options for patients with advanced disease are severely limited, screening can facilitate detection of the tumor at an early stage that is amenable to curative treatment, in particular liver transplantation [6–8]. Given a careful selection of suitable patients, five-year survival rates can improve dramatically to 70–80% after transplantation, depending on several variables such as allocation criteria, condition of the organ available and individual expertise of the respective transplant center [9]. Thus, the identification of patients at risk and implementation of structured surveillance is paramount to improving survival in HCC.

The Changing Epidemiology of HCC

The global incidence of primary liver cancer increased by 37.6% from 2006 to 2016 which has largely been attributed to population growth and aging [1, 3]. While age-standardized incidence rates decreased over 20% in countries with high incidence rates, such as China and countries in sub-Saharan Africa, a substantial increase was seen in many high socio-demographic index (SDI) countries between 1990 and 2015 [3]. Firstly introduced in the Global Burden of Disease Study in 2015, the SDI is a summary measure composed of per capita income, average educational attainment, and fertility rate that aims to identify where countries or geographic regions are situated on the spectrum of development [10]. In the United States (USA), the age-standardized HCC-related mortality per 100,000 persons increased from 3.48 in 2007 to 4.41 in 2016 [11]. Several countries in Northern and Western Europe, including the UK and Germany, reported an increase in liver cancer mortality for both sexes, while the majority of Eastern European countries reported decreasing mortality rates in 2012 [12]. Projections estimate a further increase in HCC incidence rates per 100,000 person-years by 2.69% in men and 3.19% in women in the USA from 2013 to 2030 [13]. In Switzerland, incidence rates are predicted to increase by 1.3% in men and 3.4% in women annually until 2030 [14].

These developments are partially due to changes in the prevalence of predisposing risk factors. While liver transplantation wait-listing for the indication of HCC in the USA has remained stable for HBV patients between 2003 and 2015, it has increased twofold for HCV and over tenfold in the nonalcoholic steatohepatitis (NASH) population [15]. Nonalcoholic fatty liver disease (NAFLD), defined as the presence of steatosis in $>5\%$ of hepatocytes, and resulting NASH constitute growing global health problems [16]. From 2015 to 2030, the prevalence of HCC cases due to NAFLD is expected to increase by 146%, from 10,000 to 24,900 cases, while HCC incidence is expected to increase by 137%, from 5160 to 12,240 cases, in the USA [17]. In Europe, the prevalence and incidence of HCC attributable to NAFLD is estimated to rise between 2016 and 2030, with respective increases ranging from 93 and 88% in the UK to 125% and 117% in France [18].

In 2015, an estimated 71 million were living with chronic HCV, a major global risk factor for the development of HCC [4]. In high SDI countries, HCV contributed the largest proportion of 40% to liver cancer mortality [3]. The prevalence of HCV in Europe is heterogeneous, ranging from $<1\%$ in Northern and Western European countries to $>2.5\%$ in Southern and Eastern countries [19]. In the USA, the widespread dissemination of HCV infection occurred in the 1960s and 1970s, due to contaminated blood products and injection drug use, leading to the highest prevalence of HCV in the birth cohort of baby boomers born between 1945 and 1964 [20, 21]. The substantial burden of HCC that will ensue from the aging of this large birth cohort can be modeled according to Japan, where HCV infection spread in the 1920s, likely due to injection schistosomiasis treatment, and increased exponentially after World War II [22]. HCV continues to be the largest contributor to liver cancer mortality in Japan with 69%, while overall HCC incidence has begun to decline [3, 23]. However, as new effective direct-acting antivirals (DAA) for the treatment of HCV have recently become available, widespread use will likely curb the incidence of HCV-related HCC in high SDI countries. Models predict a decrease in HCC incidence in the USA if 80% of HCV infections are treated by 2030 [13].

The globally leading risk factor for HCC is HBV infection, which affects an estimated 257 million people worldwide and accounts for around one-third of overall liver cancer associated mortality [3, 4]. HBV is the main risk factor for HCC in most countries in sub-Saharan Africa and Asia [20]. However, as new treatments for HBV have been approved and global coverage with three doses of vaccine against HBV in infancy reached 84% in 2015, the global burden of HCC due to HBV has begun to ease [3, 4]. In Taiwan, universal immunization of infants against HBV has been shown to decrease the risk of developing HCC as children and young adults [24]. The predicted decline of HCC incidence among Asian/Pacific Islanders in the USA by 2030 might be underestimated, as current models do not fully account for the effect of HBV vaccination [13].

The risk of HCC occurrence varies between ethnic populations due to modifiable risk factors. However, as these risk factors are likely to change in the coming years, persisting disparities in the susceptibility to liver injury may reveal underlying genetic predispositions. Despite similar prevalence of obesity and insulin resistance, for example, the prevalence of hepatic steatosis was markedly higher in Hispanics than in Blacks (45% vs. 24%) in subjects from a large, population-based sample in the USA [25]. A single-nucleotide polymorphism in the patatin-like phospholipase domain-containing 3 (PNPLA 3) gene, resulting in a change of codon 148 from isoleucine to methionine due to a substitution from cytosine to guanine, was found to be associated with liver fat content and has later been linked to an increased risk of HCC occurrence in NAFLD [26, 27]. Stratification by ancestry revealed a higher frequency of the allele in Hispanics (0.49) than in African Americans (0.17) [26].

Surveillance and Screening Tools

Surveillance comprises the application of diagnostic tests at pre-defined periodic intervals in subjects who are at risk of developing a specific disease. However, surveillance is feasible, cost-effective, and useful only in a context where the incidence of the disease in the target population is above a certain threshold, efficient diagnostic tests are available at a bearable cost, and effective treatments can be provided upon diagnosis [28]. Regarding hepatocellular carcinoma, current guidelines recommend biannual surveillance by ultrasound with or without alpha-fetoprotein (AFP) in high-risk patients [29, 30]. As suggested by cost-effectiveness analyses, an incidence of 1.5% per year or greater would warrant systematic HCC surveillance [31]. These recommendations are corroborated by data suggesting improved survival, a higher rate of early tumor detection and curative treatments among patients undergoing screening for HCC [7, 32]. In a French multicenter analysis of 216 patients with cirrhosis due to hepatitis B and C, compliance with HCC surveillance guidelines prior to diagnosis of HCC was associated with a significantly longer median overall survival (53.2 months vs. 25.4 months) after adjustment for lead time bias [33]. Recent findings from a case-control study within the US Veterans Affairs (VA) health care system, however, showed no significant difference in the percentage of HCC patients who underwent screening between those who died of HCC and their matched controls who survived within a 4-year period [34]. Thus, whether HCC screening as recommended today improves survival continues to be a matter of debate.

Abdominal ultrasound and AFP, which are the two most commonly used screening modalities, have several limitations. According to a recent meta-analysis, ultrasound detects early stage HCC with a sensitivity of only 47% (95% CI 33–61%), which is barely above the 42% threshold required by cost-effectiveness analysis when assuming a minimum rate of access to screening of 34% [35, 36]. While the addition of AFP measurements increased the sensitivity of early stage detection to 63%, the specificity decreased from 92% in ultrasound alone to 84% with AFP [35]. Due to false-positive or indeterminate results, screening tests with a low specificity may impose substantial physical harm on patients, including multiple CT/MRI scans and liver biopsy, as was pointed out in a retrospective cohort analysis [37]. Cost-effectiveness analyses were modeled assuming a rate of access to screening of 34%, while, according to recent data from the USA, only 2% of cirrhotic patients receive consistent surveillance according to guideline recommendations, 33% undergo inconsistent surveillance and 65% receive no surveillance [36, 38].

This suggests that HCC surveillance as carried out today is not feasible and might even be wasteful, as it largely disregards the individual risk of patients. In a Markov decision-analytic model, HCC surveillance using magnetic resonance imaging (MRI), abbreviated MRI (AMRI) and/or ultrasound in a cohort stratified by high-, intermediate- and low-risk individuals was cost-effective [39]. Hereby, only high- and intermediate-risk patients were screened, while no surveillance was performed in the low-risk cohort [39]. In the years to come, however, HCC screening might simply be carried out by multi-analyte blood tests, through assessment of levels of circulating protein and mutations in cell-free DNA [40].

Identification of Patients at Risk

Disease Severity

Cirrhosis is an important risk factor for the development of HCC and may develop in the context of chronic viral

hepatitis, metabolic, and nutritive diseases, such as alcohol abuse or NAFLD, as well as rarer causes, such as hemochromatosis [41]. Overall, 2.5–4% of patients with cirrhosis develop HCC per year [42–44]. Nevertheless, incidence rates vary greatly, depending on the underlying condition and presence of concomitant risk factors [45]. Among different etiologies of cirrhosis, viral hepatitis was associated with a twofold to sixfold increase in the incidence of HCC for each virus present [46].

The risk of HCC seems to increase with development of portal hypertension. A hepatic venous pressure gradient > 10 mmHg showed a sixfold increase in HCC incidence independently of cirrhosis [47]. Similarly, clinical features indicative of portal hypertension, such as low platelet count and varices, were associated with a higher risk of HCC [48]. Thus, patients with a low grade of fibrosis should be considered for HCC screening in the presence of portal hypertension.

While advanced cirrhosis increases the risk of HCC, screening in cirrhotic patients who are not eligible for transplantation or effective treatment due to advanced liver failure or decompensation is not cost-effective [49]. On the other hand, patients wait-listed for liver transplantation due to cirrhosis should undergo surveillance, as the presence of HCC might influence their ranking for transplantation and transplantability.

Nonalcoholic Fatty Liver Disease (NAFLD) and Metabolic Risk Factors

In comparison with chronic viral hepatitis, the incidence of hepatocellular carcinoma is markedly lower in patients with NAFLD. The incidence of HCC in NAFLD was found to be 0.44 per 1000 person-years versus 3.1 in untreated, inactive carriers of hepatitis B, 29.7 in untreated subjects with compensated cirrhosis due to hepatitis B and over 70 in Japanese patients with compensated HCV cirrhosis [46, 50, 51]. Among patients with NAFLD, a subset of patients will proceed to develop nonalcoholic steatohepatitis (NASH), which is defined as the presence of hepatocyte damage and accompanied by a higher HCC incidence rate of 5.29 per 1000 person-years [50, 52]. Given the high global prevalence of nonalcoholic fatty liver disease of over 25%, NAFLD contributes substantially to the global burden of HCC [50]. Data suggest a shorter overall survival in patients presenting with NAFLD-HCC, although this did not reach statistical significance after adjustment for lead time in patients under surveillance, suggesting later diagnosis in NAFLD-HCC patients not under regular surveillance rather than more aggressive disease [53]. Due to low incidence rates and the large number of affected individuals, general screening of patients with NAFLD is not feasible or cost-effective. Thus, finding a common denominator of NAFLD-HCC patients is crucial to improving the prognosis of this emerging disease.

HCC in non-cirrhotic patients is more often associated with NAFLD than with other etiologies [54]. Data suggest that 40–50% of HCC in NAFLD arise in the absence of cirrhosis [53, 55]. Accordingly, 55.9% of non-cirrhotic patients with NAFLD-HCC had no histological findings of fibrosis (F0), 17.6% had stage 1 fibrosis, 8.8% stage 2, and 17.6% stage 3 [56]. Stratification by stage of fibrosis might therefore not adequately identify patients at risk.

In comparison with patients with HCC due to HCV cirrhosis, patients with NAFLD-HCC were more likely to present with one or more components of metabolic syndrome, such as diabetes mellitus, arterial hypertension, and dyslipidemia [53]. In a cohort of HCC patients with NAFLD from the US Veterans Administration, more than half of whom were non-cirrhotic, diabetes, and arterial hypertension were present in 89.2% and 95.8%, respectively [57]. However, NAFLD-HCC in non-cirrhotic livers was less likely to be accompanied by obesity (52% vs. 83%) or type 2 diabetes (38% vs. 83%) compared to those with an underlying cirrhosis in a retrospective analysis [56].

Obesity and diabetes mellitus have previously been established as risk factors for HCC. Irrespective of the presence of NAFLD, patients with metabolic syndrome showed a fivefold increased risk of non-cirrhotic HCC compared to non-cirrhotic HCV patients [54]. In a Taiwanese cohort of male HBV carriers, those with ≥3 metabolic risk factors, defined as diabetes, impaired fasting glucose, obesity, hypertriglyceridemia, hypercholesterolemia and hypertension, had a twofold to threefold increased incidence of HCC (HR 2.32, 95% CI 1.18–4.54) [58]. Interestingly, one study showed a markedly increased risk of HCC for patients with obesity in early adulthood (mid-20s to mid-40s) with an estimated odds ratio of 2.6 (95% CI 1.4–4.4), while this relationship persisted in non-diabetic patients [59]. As previously mentioned, carriage of the PNPLA3 polymorphism was associated with development of HCC in patients with NAFLD as well as in obese patients [27]. However, whether this parameter can be used to identify patients at risk of HCC has to be further examined.

Alcoholic Liver Disease and Smoking

Alcohol accounts for around one-third of liver-related deaths globally [3]. In a large European cohort, the incidence of HCC due to cirrhosis in the context of alcoholic liver disease was up to 2.9 per 100 patient-years [60]. In a meta-analysis, a dose-dependent increased liver cancer risk was found for alcohol consumption, with a risk of 1.16 (95% CI 1.01–1.34) in those who consumed ≥3 drinks per day [61].

Synergistic effects with concurrent metabolic risk factors, such as diabetes and obesity, have been described for

alcohol as well as smoking [62, 63]. In a large cohort of Taiwanese male civil servants, a strong effect modification by smoking was found for the relationship between HCC and metabolic risk factors [58]. The adjusted hazard rate of HCC for smokers with ≥3 metabolic risk factors was 5.06 (95% CI 2.23–11.47) [58].

Hepatitis C Infection

The risk stratification of patients who successfully received treatment for HCV poses a challenge. Previously, a significant reduction of HCC risk was shown in patients who achieved sustained virological response (SVR) after treatment with Interferon-based therapy, while the annual incidence of HCC in cirrhotic patients remained high at 1.39% [64]. Similarly, a persisting risk has been confirmed for cirrhotic patients following SVR after DAA therapy with an annual incidence rate of 1.82 per 100 person-years [65]. Models to predict the individual risk of HCC occurrence after antiviral therapy for HCV, based on data from the Veterans Health Administration (VHA), have recently been proposed [66]. Commonly identified risk factors among these patients included higher age, low platelet count, and past alcohol intake [66, 67]. Regarding the suspicion of an increased incidence of HCC following DAA therapy, recent finding suggest that these effects might be due to differences in patient characteristics and reduced screening intensity rather than DAA therapy, suggesting that screening guided by the before-mentioned risk factors will suffice in these patients [68].

Chronic Hepatitis B Infection

The incidence rates of HCC in patients with chronic HBV infection vary widely according to disease activity and geographic region, ranging from 0.02 per 100 person-years in inactive carriers in Europe and the US, to 3.7 among patients with compensated cirrhosis in East Asian countries [69]. While HBV cirrhosis is accompanied by a markedly increased risk for HCC, risk stratification of HBV patients is further complicated by tumor formation in non-cirrhotic tissue, due to integration of viral DNA into the host genome leading to activation of oncogenic signals and carcinogenesis [70]. Environmental factors, such as dietary exposure to the carcinogenic mycotoxin aflatoxin B1, which leads to a mutation on codon 249 of the tumor suppressor gene p53 (TP53), have been shown to increase the risk of HCC in a dose-response manner among HBV carriers [71, 72]. Factors indicating virus replication and activity, such as HBeAg positivity, HBsAg level and viral load, as well as concomitant hepatitis D infection can help identify patients at increased risk for HCC [73–76].

The risk of patients receiving nucleot(s)ide analogues (NAs) for HBV infection is not well defined. A significant reduction of the annual HCC incidence rate from 2.5% per year to 0.4% was observed in a retrospective analysis of Japanese patients receiving NAs [77]. Yearly incident rates of HCC significantly declined within 5 years, from 3.22 to 0.49%, in Caucasian cirrhotic patients under NA therapy [78]. New data from a predominantly Caucasian population indicate an excellent long-term survival for patients under NAs [79]. Persistent low-level viremia under entecavir monotherapy was identified as a risk factor for HCC development in cirrhotic patients [80].

Compliance with ethical standards

Conflict of interest Naomi Lange do not have any conflicts of interest to disclose. Jean-François Dufour served as advisory committees in Abbvie, Bayer, BMS, Falk, Genfit, Genkyotex, Gilead Science, Intercept, Lilly, Novartis.

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