Review

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Epidemiology and surveillance for hepatocellular carcinoma: New trends

Amit G. Singal[1,*], Pietro Lampertico[2], Pierre Nahon[3,4,5,6]

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Summary

The burden of hepatocellular carcinoma (HCC) is highest in East Asia and Africa, although its incidence and mortality are rapidly rising in the United States and Europe. With the implementation of hepatitis B vaccination and hepatitis C treatment programmes worldwide, the epidemiology of HCC is shifting away from a disease predominated by viral hepatitis – an increasing proportion of cases are now attributable to non-alcoholic steatohepatitis. Surveillance using ultrasound, with or without alpha-fetoprotein, every 6 months has been associated with improved early detection and improved overall survival; however, limitations in implementation lead to a high proportion of HCC being detected at late stages in clinical practice. Herein, we review the current state of HCC surveillance and highlight areas for future research, including improved risk stratification of at-risk patients, surveillance tools with higher sensitivity and specificity for early HCC, and interventions to increase surveillance utilisation.

[1]*Division of Digestive and Liver Diseases, UT Southwestern Medical Center, Dallas, TX, USA*;
[2]*CRC "A. M. and A. Migliavacca" Center for the Study of Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy*;
[3]*Centre de Recherche des Cordeliers, Sorbonne Universités, Université Paris Descartes, Université Paris Diderot, Université Paris, Paris, France*;
[4]*Functional Genomics of Solid Tumors, USPC, Université Paris Descartes, Université Paris Diderot, Université Paris, Paris, France*;
[5]*Service d'hépatologie, Hôpital Jean Verdier, Hôpitaux Universitaires Paris-Seine-Saint-Denis, Assistance-Publique Hôpitaux de Paris, Bondy, France*;
[6]*Unité de Formation et de Recherche Santé Médecine et Biologie Humaine, Université Paris 13, Communauté d'Universités et Etablissements Sorbonne Paris Cité, Paris, France*

Key points

The large majority of HCC cases occur in patients with chronic liver disease, with cirrhosis being the main risk factor.

Introduction

Liver cancer is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related death worldwide, after lung, colorectal, and stomach cancer.[1] Liver cancer is a highly fatal tumour, with most cases detected at late stages and an incidence-to-mortality ratio that approaches 1. For example, there were approximately 854,000 new liver cancer cases in 2015, compared to an estimated 810,000 liver cancer-related deaths per year.[2] Hepatocellular carcinoma (HCC) represents about 75–85% of primary liver cancers[3] and constitutes a major health problem worldwide.

Incidence

The worldwide incidence of HCC is heterogeneous because of the variable prevalence of underlying risk factors. It is estimated that 72% of cases occur in Asia (more than 50% in China), 10% in Europe, 7.8% in Africa, 5.1% in North America, 4.6% Latin America and 0.5% in Oceania.[4] Fig. 1 shows the estimated age-standardised incidence rates (ASIRs) for liver cancer in the world in 2018. The highest ASIRs per 100,000 occur in Eastern Asia (17.7), with Mongolia (93.4) having the highest ASIR in this region and the world, followed by South-East Asia (13.3), and Africa (8.4), with Egypt (32.2) and Gambia (23.9) having the highest ASIRs in Africa. The lowest ASIRs are observed in South Central Asia (2.5), followed by Central and Eastern Europe and Western Asia (equally about 4.0).[5]

Mortality

Age-standardised mortality rates (ASMRs) from HCC in 2018 are also highest in Eastern Asia (16.0) and Northern Africa (13.9), followed by South Eastern Asia (13.2). The lowest ASMR is observed in South Central Asia (2.3), followed by Central, Northern, and Eastern Europe and Western Asia (around 3.8–4.0). Mongolia and Egypt have the highest ASMRs, while the lowest are in Morocco and Nepal, countries with low ASIRs. Worldwide the ASMR is close to ASIR, reflecting the fact that HCC is a deadly disease.[6]

Aetiology

The large majority of HCC cases occur in the setting of chronic liver disease, with cirrhosis being the primary risk factor for HCC, independent of liver disease aetiology. It is estimated that one-third of cirrhotic patients will develop liver cancer during their lifetime,[7] with a 1–8% annual incidence reported in long-term follow-up studies (*e.g.* 2% in HBV-infected cirrhotic patients and 3–8% in HCV-infected cirrhotic patients).[8] The incidence of HCC appears lower in alcohol-related and non-alcohol steatohepatitis (NASH)-related cirrhosis than active viral hepatitis but the incidence appears to be greater than 1.5% across cirrhosis aetiologies.

Hepatitis B virus (HBV) is the leading cause of incident cases of liver cancer and deaths in the world (33%), followed by alcohol (30%), hepatitis C virus (HCV) (21%) and other causes (16%). The contribution of different aetiologies to HCC incidence varies markedly between countries and regions and is summarised in Table 1. In Africa and East Asia, the largest population attributable fraction is caused by HBV (60%); however, in the

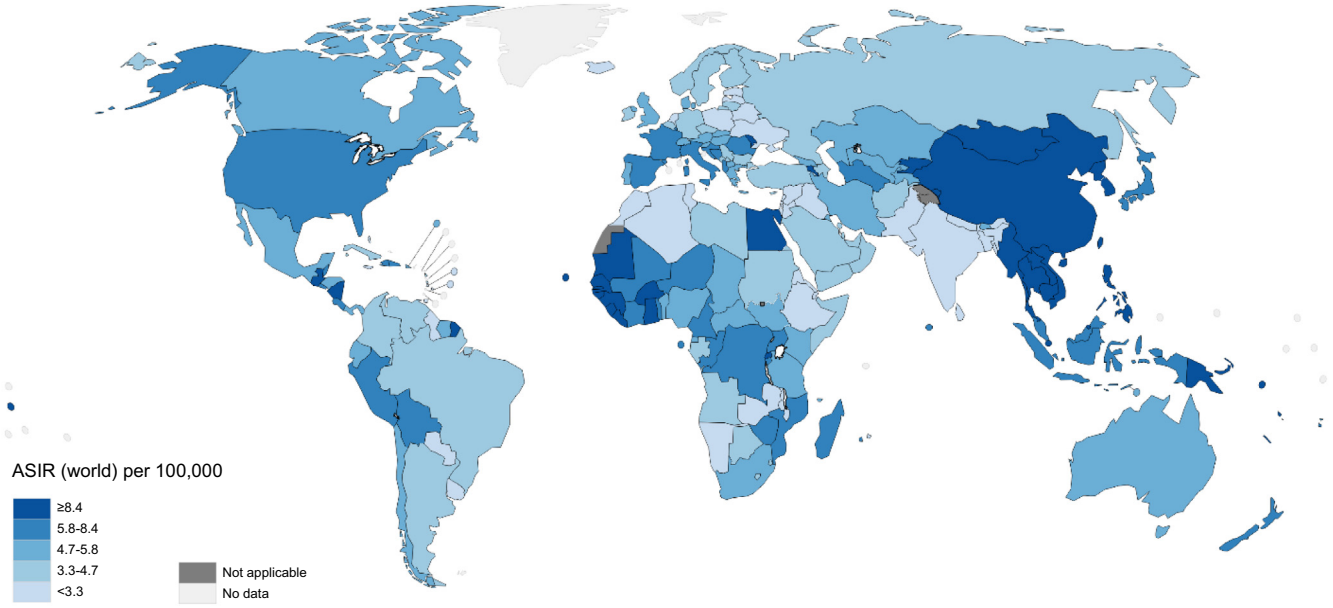

Fig. 1. Worldwide age-standardized HCC incidence rates, 2018. Data source: GLOBOCAN 2018. Graph production: IARC (http://gco.iarc.fr/today), World Health Organization. Accessed 24 October 2019. ASIR, age-standardized incidence rate; HCC, hepatocellular carcinoma.

Table 1. Geographical distribution of risk factors for primary liver cancer.

Variables	Alcohol (%)	Hepatitis B (%)	Hepatitis C (%)	Others (%)
Global	30	33	21	16
Europe				
Western	32	13	44	10
Central	46	15	29	10
Eastern	53	15	24	8
America				
North America	37	9	31	23
Andean Latin America	23	45	12	20
South Latin America	42	6	41	11
Asia				
East Asia	32	41	9	18
Asia-Pacific	18	22	55	6
South-East Asia	31	26	22	21
Africa				
North Africa, Middle East	13	27	44	16
Southern (sub-Saharan)	40	29	20	11
Western (sub-Saharan)	29	45	11	15
Oceania	16	38	19	27

Contribution of hepatitis B, C, alcohol and others causes on absolute liver cancer deaths, both sexes, globally and by region 2015 (3). Data refer to all primary liver cancers (hepatocellular carcinoma, intrahepatic cholangiocarcinoma and liver cancer of mixed differentiation).

Western world only 20% of cases can be attributed to HBV infection, and chronic HCV is the most common underlying liver disease aetiology.[2] Among HBV-infected individuals, HBeAg seropositivity,[9] high viral load[10] and genotype C[11] are independent predictors of HCC development. Although prior studies among HCV-infected patients reported similar risk factors, *e.g.* HCV genotype, the strongest determinants of HCC risk in these patients are currently the presence (*vs.* absence) of cirrhosis and attaining sustained virological response (SVR). Guidelines uniformly recommend surveillance in patients with HCV-related cirrhosis but differ on HCC risk and recommendations for HCC surveillance in HCV-infected patients with F3 fibrosis;[12–14] however, a recent cost-effectiveness analysis suggests that this practice is likely not cost-effective in those without cirrhosis.[15]

Implementation of infant HBV immunisation programmes in many countries in East Asia is expected to lower HBV-related HCC in the future, as demonstrated in Taiwan where annual HCC incidence significantly decreased from 0.92 per 10^5 persons in an unvaccinated cohort of patients to 0.23 per 10^5 persons in a vaccinated birth cohort.[16] However, there are several countries which have yet to implement universal HBV vaccination, so many individuals are still infected with HBV (approximately 257 million in 2015), mostly in Asia and sub-Saharan Africa.[17] Unfortunately, a vaccine for HCV does not exist, so primary prevention of HCV-related HCC is not possible. Among

* Corresponding author.
Address: Division of Digestive and Liver Diseases, UT Southwestern Medical Center, 5959 Harry Hines Blvd, POB 1, Suite 420, Dallas TX 75390-8887, USA.
Tel.: +1 214 645 6111; fax: +1 214 645 6114.

E-mail address: amit.singal@utsouthwestern.edu (A.G. Singal).

Key points

In epidemiological studies, coffee consumption, aspirin use, and metformin treatment have been shown to reduce the incidence of HCC in patients with diabetes.

those with active infection, antiviral therapies are effective in reducing HCC incidence although they do not eradicate the risk, in both HBV- and HCV-infected patients.[18–20] Among HCV-infected patients the risk of developing HCC significantly declined from 6.2% to 1.5% with interferon-based SVR[19] and a similar reduction is observed for SVR from direct-acting antiviral agents.[20] Despite improvement, patients with cirrhosis prior to SVR remain at high risk of HCC, so surveillance should be continued.[21]

Alcohol consumption and the resulting cirrhosis seem to have a causal relationship in the development of HCC.[22] In France, the estimated HCC incidence in patients with alcoholic cirrhosis was 2.9 per 100 patient-years in a cohort of 652 French patients during a median follow-up of 29 months.[23] An increased risk of developing HCC has been reported for most parts of the world (with the exception of Northern Europe), including France[24] and Spain.[25]

There is growing evidence that non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) contribute to HCC development, and are becoming an increasingly common cause of HCC worldwide. It is estimated that about 10–30% of NAFLD cases progress to cirrhosis, and in the United States alone approximately 6 million people have NASH.[26] Although patients with NASH appear to have a lower risk of HCC than patients with HCV-related cirrhosis, the annual incidence is likely between 1–2%. In a large cohort study of 4,235 patients with NASH cirrhosis from the Veterans Affairs health system in the United States, the incidence of HCC was determined to be 1.06 per 100 person-years.[27] Although patients with NAFLD are at a lower risk of developing liver cancer than those with NASH cirrhosis, the high number of people with NAFLD make it one of the major causes of HCC. There have now been several cohort studies that have shown over one-fourth of NASH-related HCC can occur in the absence of cirrhosis,[28,29] which is significantly higher than proportions seen in other liver diseases.[30] However, the annual incidence rate of HCC in non-cirrhotic NASH appears to be low. Data from the Veterans Affairs health system demonstrated an incidence of HCC of only 0.008 per 100 person-years among a cohort of 292,366 patients with non-cirrhotic NAFLD.[27] Similarly, data from Taiwan demonstrated 1-, 3-, and 5-year cumulative incidences of only 0.2%, 0.8%, and 1.0%.[31] However, a recent systematic review of this literature highlighted several notable limitations of the current literature including heterogeneous definitions for NAFLD, differential proportions of patients with metabolic syndrome, heterogeneous definitions for cirrhosis, ascertainment bias given intermittent surveillance and selection/referral bias.[32] Therefore, the impact of metabolic liver disease on the epidemiology of HCC is likely to be underestimated. Components of the metabolic syndrome, such as diabetes and/or obesity, are emerging risk factors for HCC and may increase HCC risk if present with other chronic liver diseases, even in the absence of a NAFLD diagnosis. Obesity might account for about 16% of HCC cases in Europe, according to the EPIC study,[33] while both obesity and/or diabetes account for about 37% of HCC in the US.[34] Based on current data, HCC risk is sufficient to justify HCC surveillance in patients with NASH cirrhosis; however, HCC surveillance is not recommended in those with non-cirrhotic NAFLD given the low annual incidence rate.

Patients with other, less common causes of cirrhosis including primary biliary cirrhosis, autoimmune hepatitis, and haemochromatosis are also at an increased risk of HCC. Patients with haemochromatosis who progressed to advanced fibrosis/cirrhosis are at extremely high risk and develop HCC in up to 45% of cases[35,36], with a higher incidence in those with acute hepatic porphyria and porphyria cutanea tarda.[37,38]

Among patients with cirrhosis, there is a differential distribution of cases by several sociodemographic factors. HCC has a strong male predominance for incidence and mortality, with a male-to-female ratio exceeding 2.5 for both.[2] This differential distribution by sex is believed to be related to a clustering of risk factors among men, as well as a potential effect of androgens on HCC risk. Similarly, several studies have reported higher incidence and mortality rates among racial/ethnic minorities in the United States, with higher incidence rates among racial/ethnic minorities than non-Hispanic whites.[39]

Finally, there are important environmental risk factors for HCC. For example, dietary intake of aflatoxin B1, which originate from fungal contaminations of staple foodstuffs, is a relevant co-factor for HCC development in parts of Africa and Asia. Aflatoxin B1 exposure is strongly correlated with *TP53* mutations (codon 249) and HCC development in HBV-infected individuals.[40] Several epidemiological studies have also revealed an increased risk of developing HCC among smokers, with a meta-analysis reporting an adjusted RR of 1.5 (95% CI 1.37–1.67) compared to non-smokers.[41]

Several epidemiological studies have addressed the topic of HCC prevention in the general population and in patients with chronic liver disease. Coffee consumption, aspirin use and metformin treatment have consistently been shown to reduce the HCC incidence in patients with diabetes.[13,42,43] The highest evidence has been produced for coffee consumption by means of case-control studies in Japanese patients with HCV and a hospital-based control study among Italian patients with a variety of liver disease aetiologies. These findings have also been confirmed in cohort studies performed in Japan and Southern Europe, as well as a meta-analysis.[13,44–47]

Trends

Between 1990 and 2015, liver cancer incidence increased by 75% worldwide. These data reflect changes in aetiology, population age distribution, population growth, and ASIRs.[2] During this period a significant increase in HCC age-standardised incidence (per 100,000 persons) due to HCV (+15.7%) was observed, while HBV-related HCC significantly decreased (−18.9%) and no significant changes were observed for HCC due to alcohol (+13.5%) and other causes (−12.3%).[2] Despite a decrease in ASIRs for HCC related to HBV and other causes, overall incident HCC cases have increased because of demographic changes, namely population growth and aging.[2] Based on current trends, the number of new cases of, and deaths caused by, liver cancer are projected to increase from 841,080 and 781,631 in 2018, to 1,361,836 and 1,284,252 in 2040, representing changes of +62% and +64%, respectively.[48]

There is geographic variation in these temporal trends. ASIRs have increased in many high socio-demographic index countries like North America (USA, Canada), Australia, New Zealand and most European countries (*i.e.* Austria, Denmark, Germany, Greece, Ireland, Portugal, Norway, Spain, Switzerland, and United Kingdom); conversely, some countries with high incidence rates like China and countries in Eastern and Western sub-Saharan Africa have experienced a more than 20% decrease.[2] Declines in ASIRs have also been observed in Japan, where a decline in HCC incidence has been noted for the first time since 1990,[49,50] and in some countries in Europe (*i.e.* Finland, France, Italy, the Netherlands, and Sweden).[51]

Along the same line is a recent report evaluating projections of primary liver cancer occurrence in 30 countries worldwide,[52] which predicts the percentage change in ASIR over a 25-year period, from 2005 to 2030, increasing >30% among men in 15 countries and among women in 8 countries. The largest rate increases among men are predicted in Norway (2.9% per annum), US whites (2.6%), Canada (2.4%), and the Russian Federation (2.2%). Equivalent increases in primary liver cancer among women are predicted in fewer countries, with the greatest increases expected among US blacks (4.0%), Switzerland (3.4%), and Germany (3.0%). In contrast, a decrease in liver cancer among men is predicted in Japan (23.1%), China (22.1%), Singapore (21.6%), Slovakia (21.4%), the Czech Republic (21.0%), and Estonia (20.6%), while the largest decreases among women are predicted in Japan (22.3%) and Denmark (21.8%).

The predicted increases in incidence mainly reflect population growth and aging in most countries, as well as changes in risk factors. Changing distributions of risk factors, especially HBV, HCV, alcohol consumption, and obesity, could alter future trends and projections. Based on the predicted declines in the prevalence of HBV and HCV infections, mainly due to HBV immunisation and increased efforts to screen and treat patients with active HCV, the importance of non-viral risk factors for HCC is expected to increase in the future, mainly due to NAFLD. In the United States, it was estimated that the incidence of HCC due to NAFLD would increase by 122% between 2016 and 2030, from 5,510 to 12,240 cases.[53]

HCC surveillance data and intervals

Cancer surveillance programmes aim to detect tumours at an early stage when they are amenable to curative therapy that is known to improve survival,[54] The evidence highlighting a survival benefit associated with HCC screening in patients with cirrhosis remains controversial.[55] Apart from numerous methodological biases discussed below, analysis of the literature shows that negative studies often underscore inappropriate or suboptimal implementation of screening procedures rather than failure of surveillance programmes to be translated into survival benefit.[56] The only randomised controlled trial supporting HCC surveillance with 6-monthly abdominal ultrasound was performed in more than 18,000 Chinese patients and showed a 37% reduction in mortality risk in screened patients.[57] However, this trial was conducted in an HBV-infected patient population and it is unclear if these results would apply to patients with cirrhosis given increased nodularity, which could impact surveillance effectiveness, as well as a higher competing risk of liver-related mortality. Because the implementation of trials comparing screening versus no surveillance would not be ethical,[58] the level of evidence mostly relies on retrospective observational studies which have concluded that surveillance for HCC was an independent predictor of survival.[59–63] More recently, the long prospective follow-up of patients with compensated viral cirrhosis showed that patients who respected the recommended 6-month screening interval had a higher proportion of HCC detected at an early stage, which translated into a survival benefit due to more frequent implementation of first-line curative procedures.[64] However, numerous limitations and biases affecting observational studies dedicated to cancer screening must be acknowledged. Among them, lead-time bias suggests that a given proportion of the survival benefit could be ascribed to earlier diagnosis due to surveillance. In addition, length time bias supports that tumours diagnosed early in the setting of surveillance programmes might differ in their prognosis from tumours diagnosed later. The most recent studies assessing the impact of HCC screening on outcomes usually considered these biases in an attempt to reinforce the strength of their conclusions.[65]

Western recommendations support a 6-month screening interval, based on HCC volume doubling-time, which is estimated to be around

Key points

The incidence of HCC is expected to increase in the coming years, reflecting population growth and aging.

6 months.[66] In order to minimise the risk of detecting HCC at an advanced stage, a 3-month interval has been proposed by Japanese guidelines for specific groups considered at higher risk.[67] However, a French randomised trial had previously compared intervals of 3 and 6 months in more than 1,200 cirrhotic patients, and concluded that surveillance performed every 3 months, detected increased small-size focal lesions compared with ultrasound every 6 months but did not improve detection of early HCC and did not translate into survival benefits.[68] Similarly, a large retrospective study assessed the impact of different surveillance intervals in patients at risk of HCC.[69] Shorter ultrasound screening intervals were associated with reduced overall mortality in these patients, and as a whole provided additional arguments to support the 6-month screening interval as the optimal cut-off for HCC surveillance.

Surveillance tests

Abdominal ultrasound has been the historic cornerstone of HCC surveillance and continues to be recommended as the primary surveillance test by the AASLD, EASL, and APASL. It has several advantages including being cheap, readily available, and safe with minimal direct physical harms. Although ultrasound has an acceptable sensitivity of 84% (95% CI 76–92%) for detecting HCC at any stage, its sensitivity for detection of early stage HCC is significantly lower at only 47% (95% CI 33–61%).[70] Further, its effectiveness can be affected by operator expertise as well as several patient-level factors such as obesity and liver disease severity, leading to wide variations in its sensitivity between centres and patients.[71–73] The reported lower sensitivity of ultrasound in patients with obesity and non-viral liver disease is particularly concerning in light of epidemiologic shifts, with an increasing proportion of HCC related to underlying NASH. However, there are few data specifically evaluating surveillance effectiveness among cohorts with emerging risk factors, such as those with NASH and post-SVR HCV infection.

Given these concerns, alternative imaging modalities, such as CT or MRI, are increasingly being used in clinical practice;[74] however, there are currently limited data supporting routine use of cross-sectional imaging for HCC surveillance. A small single-centre randomised trial comparing CT and ultrasound-based surveillance among 163 patients with cirrhosis failed to find a significant difference in early detection (62.5.5% *vs.* 55.5%, $p = 0.93$) or HCC-related mortality (8.8% *vs.* 6.0%, $p = 0.46$) despite significantly higher costs in the surveillance CT group ($57,383 *vs.* $17,041 per HCC detected).[75] Subsequently, a recent retrospective cohort study including 636 HBV-infected patients found that patients who underwent surveillance using alternating CT and ultrasound every 6 months had improved early HCC detection compared to those who underwent ultrasound-based surveillance (HR 2.52, 95%CI 1.41–4.51); however, these data are limited by potential selection bias and residual confounding so still require prospective validation.[76] Finally, Kim and colleagues conducted a prospective cohort study comparing MRI-based and ultrasound-based surveillance among 407 patients with cirrhosis (predominantly HBV-related) and found MRI-based surveillance had a significantly higher sensitivity for early HCC detection than ultrasound (83.7% *vs.* 25.6%).[77] However, further data about MRI performance in non-HBV patients and its cost-effectiveness are still needed prior to routine use of surveillance MRI in clinical practice. Other concerns about potential physical harms (radiation and contrast exposure), financial harms (costs), and limited radiologic capacity may also limit routine use of CT or MRI for HCC surveillance in all patients with cirrhosis. Early studies evaluating alternative imaging strategies, such as abbreviated MRI protocols, have suggested high sensitivity for early HCC detection, approaching that of diagnostic MRI;[78–80] however, these data are limited by selection bias and verification bias, which may overestimate the accuracy of abbreviated MRI. Until data evaluating these novel imaging techniques in larger cohorts mature, ultrasound remains the standard radiographic surveillance modality.

Therefore, there has been increasing interest in serum biomarkers that may improve sensitivity for early HCC detection. The best studied biomarker to date remains alpha-fetoprotein (AFP), which has garnered limited enthusiasm given poor sensitivity for HCC when used alone. However, a meta-analysis of studies that directly compared the performance of ultrasound alone versus ultrasound plus AFP for early HCC detection found concomitant use of ultrasound and AFP improved early HCC detection compared to ultrasound alone, with sensitivities of 63% (95% CI 48–75%) and 45%, (95% CI 30–62%), respectively.[70] The improved sensitivity was offset by a decrease in specificity (84% *vs.* 92%, RR 1.08, 95% CI 1.05–1.09), although the clinical significance of this decrease is thought to be minimal. The diagnostic odds ratio, which accounts for sensitivity and specificity, of the 2 tests in combination was higher than that of ultrasound alone. Further, several methods have been proposed to minimise false-positive results of AFP. First, using the trend of AFP values, rather than a single test result at a fixed threshold, better reflects how AFP is interpreted in clinical practice and can more accurately identify patients with early stage HCC.[81–82] Patients with consistent increases in AFP level, even if below 20 ng/ml, can be concerning and prompt cross-sectional imaging, whereas stable to decreasing AFP levels, even if greater than

20 ng/ml, would be reassuring and may be monitored instead of requiring diagnostic evaluation. Second, AFP is traditionally interpreted at a cut-off of 20 ng/ml for all patients with cirrhosis, despite recognition that it is often elevated in the absence of HCC among patients with viral hepatitis.[83] Therefore, use of different AFP cut-offs by liver disease aetiology can improve specificity, with 1 study suggesting a higher cut-off of 59 ng/ml in patients with cirrhosis caused by viral hepatitis and a lower cut-off of 11 ng/ml in those with non-viral cirrhosis.[84] Finally, there has been increasing interest in developing AFP-adjusted algorithms to improve its accuracy for early HCC detection. For example, an HCC early detection screening (HES) model that incorporates the rate of AFP change along with the most recent value of AFP, age of the patient, alanine aminotransferase blood level, and platelet count is associated with improved sensitivity for early HCC detection compared to the current standard of care.[85]

Due to intra-tumoral heterogenicity in HCC, there has been increasing recognition that a single biomarker may not be sufficient, and that a combination of biomarkers may be needed to optimise sensitivity for early HCC detection. GALAD, which includes gender, age, lectin-bound AFP % (AFP-L3%), AFP, and des-gamma carboxy prothrombin (DCP), is one of the best studied biomarker panels to date. In a multinational phase II study with 6,834 patients (2,430 HCC and 4,404 chronic liver disease), GALAD achieved sensitivities ranging from 60% to 80% for early HCC detection.[86] Another panel including AFP, fucosylated kininogen, age, gender, alkaline phosphatase, and alanine aminotransferase demonstrated a c-statistic of 0.97 (95% CI 0.95–0.99) for early HCC detection in a small phase II biomarker study of 162 patients (69 early HCC, 93 cirrhosis).[87] Finally, a methylated DNA marker panel had a c-statistic of 0.96 (95% CI 0.93–0.99), with a sensitivity exceeding 90%, for early HCC detection in a phase II study with 146 patients (95 HCC and 51 cirrhosis).[88] Similar to individual biomarker studies, these data are promising but still require validation in large phase III biomarker studies.

Potential surveillance harms

As for all screening programmes, HCC surveillance might cause objective or subjective discomfort encompassing: i) depression or anxiety during the screening process, ii) financial or physical harms resulting from investigation of false-positive or indeterminate results and iii) overdiagnosis and overtreatment of a tumour that never would have progressed to clinical attention in the absence of screening, although the latter is likely a rare situation in the case of HCC.[89–91] Overall, the risk of these potential harms when deciding to perform recall procedures for a focal lesion and/or elevated serum biomarker has to be weighed against the dismal prognosis in the case of unscreened liver cancer and the possibility of remission from curative procedures of a tumour detected during surveillance.

All guidelines recommend the performance of contrast-enhanced imaging techniques when a focal lesion, larger than 1 cm, is detected by ultrasound.[12–14] CT scans lead to radiation exposure and might be responsible for potential renal toxicity due to contrast injection.[92] While MRI scans cause no radiation exposure, the test is costly, a contrast injection is still required, and it can be a particular cause of distress for patients.[93] Recent data suggest a risk of gadolinium accumulation, although the long-term clinical consequences of this phenomenon are currently unknown. In cases of an atypical radiologic finding, a liver biopsy of the lesion is recommended. The risk of false negative biopsies are common in clinical practice, particularly in the case of small lesions, and may lead to delays in both diagnosis and treatment.[94] Tumour seeding along the biopsy tract is a rare event (1–5%), with important consequences as it may preclude the implementation of subsequent curative procedures such as ablation, resection or transplantation.[95] Finally, the risk of bleeding is considered low but can be life-threatening.[96]

A recent report suggested that false-positive or indeterminate results are likely frequently observed among patients included in HCC surveillance programmes.[97] This study included 680 cirrhotic patients, among whom 78 (11.5%) developed HCC over a 3-year period. As a measure of screening benefit, it was noted that 48 (61.5%) of the HCCs were identified by surveillance ultrasound and/or AFP. However, surveillance harm events over the same period, defined largely as "unnecessary testing", were identified in 187 (27.5%) patients and nearly 10% had moderate-to-severe harm, defined as repeated imaging and/or invasive testing such as a biopsy. Of note, some patients in this study had diagnostic evaluation for indeterminate surveillance tests, such as sub-centimetre lesions on ultrasound, suggesting surveillance harm could have been mitigated by closer observation of guideline recommendations. These data were recently confirmed in another single-centre study, which similarly found nearly 20% of patients underwent diagnostic testing for indeterminate lesions detected as part of an HCC surveillance programme.[98] Although subjective discomfort was not assessed in these studies, the results compensate for the lack of data regarding surveillance-related harms highlighted by most reports, which have mostly focused on the potential benefits of HCC surveillance.

Implementation of and compliance to surveillance programmes

Numerous studies from the West suggest that less than 30% of patients with cirrhosis are included in

Key points

There has been an increasing interest in serum biomarkers for early HCC detection, although it is accepted that a combination of markers may be required for optimal diagnostic accuracy.

Key points

The potential benefits of surveillance programmes must be weighed against the potential harms of screening, while also considering the severe consequences of late HCC diagnosis.

Key points

HCC surveillance is under-utilised in clinical practice, which can decrease its effectiveness – thus, improving utilisation is a target for intervention efforts.

HCC surveillance programmes and actually receive semi-annual screening.[99–101] Factors explaining low adherence to HCC screening are multiple. Access to care seems to impact HCC screening, in particular for uninsured patients and African Americans in the US.[102] In addition, it is suspected that only 20–50% of cirrhotic patients are seen by hepatologists or gastroenterologists, who are usually inclined to include their patients in screening programmes. In this setting, the majority of cirrhotic patients are followed by primary care providers, in whom knowledge and beliefs regarding HCC surveillance are usually less developed.[103–105] In a recent US study, a survey of 1,000 primary care providers showed that most practitioners see patients with cirrhosis, but only a minority enrol them in surveillance protocols, which could be related to suboptimal knowledge of effective HCC therapy options.[106]

Patient adherence and compliance to surveillance also seem to be a determinant. In this setting, based on the prospective follow-up of a large cohort of 1,671 patients with compensated viral-induced cirrhosis included in protocolised screening procedures, an impaired compliance to the 6-month rule was observed in nearly 40% of the 216 patients who were diagnosed with HCC during a nearly 60-month follow-up.[64] Such an observation is particularly worrisome when considering that only patients with viral-related cirrhosis (usually more prone to be compliant) who accepted long-term, periodical follow-up, were recruited. It is possible, if not likely, that adherence to surveillance regimens may be lower in patients with alcohol- or NASH-related cirrhosis.[107] Similarly, patients with a history of HCV-related cirrhosis remain at risk of HCC after SVR but may not be followed as closely and may therefore be more prone to lapses in surveillance. Further data characterising surveillance utilisation and barriers to surveillance in cohorts with these emerging risk factors are needed.

Overall these prospective analyses revealed a survival advantage associated with compliance with HCC screening guidelines after correction for lead-time bias. Indeed, respect for the 6-month screening rule was associated with early HCC diagnosis, allocation of curative treatment and longer lead-time adjusted overall survival. In this context, deciphering the mechanisms explaining lower compliance in some patients is pivotal. Patient knowledge, attitudes, and perceived barriers were recently assessed through a survey performed in a tertiary American centre and were correlated with receipt of surveillance during a 1-year period.[108] Overall, this study demonstrated that surveillance rates were higher in patients displaying high levels of cirrhosis/HCC-related knowledge; conversely, the quality of screening was impaired by several pragmatic aspects reported as "barriers" including difficulty with the scheduling process, costs of surveillance testing, and transportation difficulties. Finally, the strongest argument highlighting the impact of patient knowledge is derived from an aborted surveillance trial, in which it was demonstrated that a randomised study comparing HCC screening versus no surveillance was not feasible once informed consent had been provided.[58]

Perspectives and areas of research

Optimising HCC surveillance is one of the major challenges our community will have to deal with in order to improve the dismal prognosis of this cancer. Increasing uptake and refining strategies to tailor personalised management are the cornerstones that must guide our action (Fig. 2). The latter must be scientifically implemented and evaluated in the forthcoming years; furthermore, the evolution of healthcare and medico-economic contexts characterised by limited resources must be accounted for.

Risk stratification, cost-effectiveness and personalised screening

All patients with cirrhosis do not have the same risk of developing HCC and it remains difficult to assess the specific risk at an individual level.[109] Furthermore, and as mentioned earlier, despite enrolment in surveillance programmes, some patients are diagnosed with advanced HCC irrespective of their compliance, particularly because of the poor sensitivity of ultrasound. Such pitfalls could be overcome by using more sophisticated contrast-enhanced imaging techniques such as MRI or new circulating biomarkers, which are useful for HCC prediction as well as early detection. However, implementing such costly surveillance programmes may not be cost-effective in certain subsets of cirrhotic patients because of their particularly low annual incidence of HCC, for example in the case of cirrhotic patients with controlled or eradicated HBV-/HCV-infection.[106,64,107,108,58,109,110] In this setting, personalised assessment of the individual risk of HCC and refinement of screening policies might be discussed. Until now, various HCC scoring systems have been based on the combination of routine clinical features to stratify cirrhotic patients into various HCC risk classes.[111] However, it is unclear if clinical features can accurately risk stratify patients in isolation or if other features such as genomics or molecular signatures are needed.[112–114] Further, it is unclear if these risk stratification tools could be applied to patients with non-cirrhotic NAFLD to identify a subgroup in whom HCC surveillance may be cost-effective. Based on the stratification into low-, intermediate- or high-HCC risk groups, it is tempting to speculate that adaptation of screening strategies might optimise both cost-effectiveness and the allocation of limited medical resources. In this context, the intensification of screening

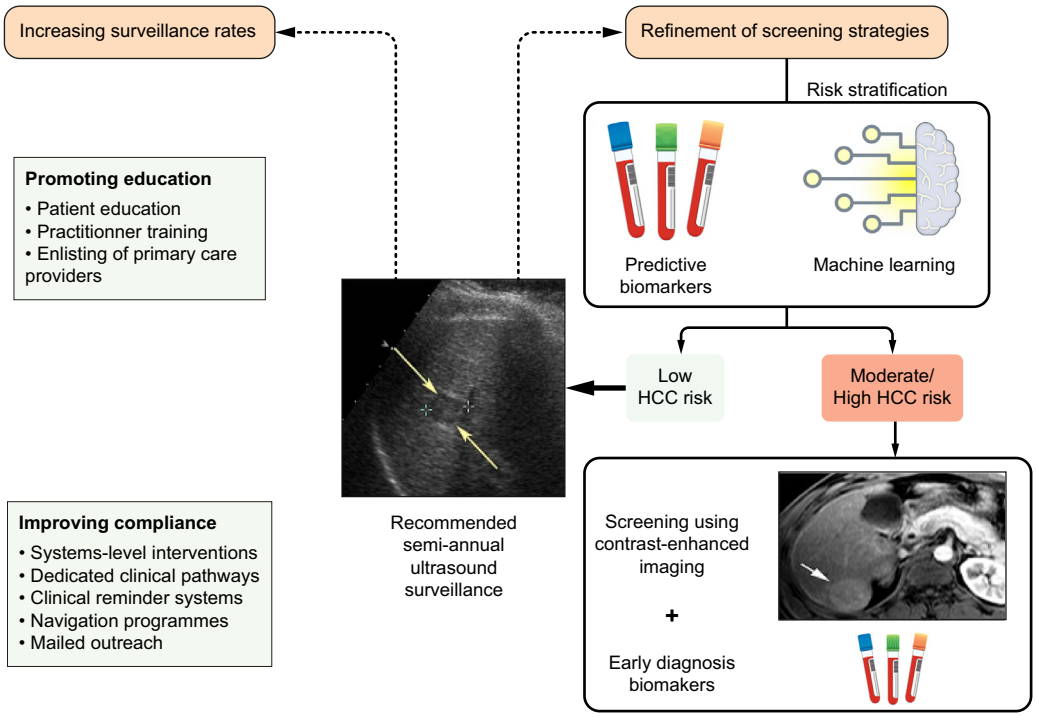

Fig. 2. Potential interventions to increase HCC surveillance effectiveness. HCC, hepatocellular carcinoma.

programmes in intermediate- or high-risk groups is a timely challenge in view of the changing epidemiology of chronic liver disease: using expensive but highly sensitive imaging techniques such as MRI or performing sequential assessment of circulating biomarkers yet to be discovered might then be justified in populations at the highest risk of HCC.[115]

Development of new biomarkers for early diagnosis

Despite improved accuracy compared to ultrasound alone, it is clear that a surveillance strategy of ultrasound and AFP remains far from where we need to be. In fact, the surveillance strategy of ultrasound with AFP still misses approximately one-third of HCC at an early stage. A number of novel biomarkers, such as DCP and AFP-L3, have been promising in phase II studies but still require validation in larger phase III cohort studies.[86] Cell free DNA released from tumour cells may be detected in peripheral blood samples and is another promising biomarker; however, it is also in the early phases of evaluation for surveillance, as its unclear if it will be found in sufficient quantities in patients with early stage tumours.[116] The development of large prospective cohorts with stored biobanks of longitudinal serum and plasma samples, such as the Early Detection Research Network (EDRN) Hepatocellular cancer Early Detection Study (HEDS) and Cancer Prevention Research Institute of Texas (CPRIT) Texas HCC Consortium (THCCC) cohorts, should facilitate phase III validation of these biomarkers in the near future.[117] Such efforts are also being initiated in Europe, with the constitution of the STHEPBIO consortium, which will encompass several prospective cohorts of cirrhotic patients with adjoining sequential biobanks from France, Italy, Belgium and Spain.

Intervention to increase surveillance rates

Optimising HCC surveillance will likely necessitate the creation of specific networks involving physicians, patients and healthcare systems. Improving patient education using dedicated tools encompassing the intervention of trained personnel, websites, patient group sessions, education screencasts, and smart phone applications must be encouraged. Involving patients in the decision-making process, in the setting of the aforementioned personalisation of screening programmes, is also strongly recommended. Integrating HCC surveillance into complete work-up sessions mixing diverse interventions (nutritionists, alcohol liaison service, portal hypertension screening) into one-stop clinics might facilitate clinical pathways and ultimately favour compliance in the long term. The intensification of specific interventions aimed at improving compliance are also needed. For instance, mailed outreach strategies and patient navigation have been proven to successfully increase HCC surveillance uptake.[118,119] In the same line, implementing clinical reminder systems for physicians seems to positively impact the respect for surveillance timeframes in routine practice[120]. Finally, enlisting primary care providers in HCC surveillance through reinforced partnership and training programmes might also facilitate screening uptake[106].

However, these interventions, particularly when implemented in broad populations followed by primary care providers alone, still have surveillance rates below 50%, highlighting the need for more intensive intervention strategies in the future.

Conclusions

The global incidence and mortality of HCC is rising, particularly in the US and Europe. Given the strong association between early detection and survival, improving uptake and performance of HCC surveillance must be defined as a priority for our community. Our actions will benefit from improved risk stratification of at-risk patients, discovery of more sensitive and specific surveillance tools (*e.g.* circulating blood-based biomarkers and new imaging techniques) and implementation of interventions to increase surveillance utilisation that involve a broader range of physicians and patient participation. Healthcare systems will need to adapt to the changing epidemiology of chronic liver disease and the associated economic burden, in order to move towards a personalised approach aimed at increasing the percentage of patients with HCC eligible for curative procedures. This could be the most effective action to improve the prognosis of this difficult-to-treat cancer.

Abbreviations

AFP, alpha-fetoprotein; ASIRs, age-standardised incidence rates; ASMRs, age-standardised mortality rates; DCP, des-gamma carboxy prothrombin; HCC, hepatocellular carcinoma; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SVR, sustained virological response.

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Conflict of interest

Amit G. Singal has has served on advisory boards for Gilead, Abbvie, Bayer, Eisai, Bristol Meyers Squibb, Wako Diagnostics, and Exact Sciences. He serves as a consultant to Bayer, Eisai, Exelixis, Roche, Exact Sciences, Glycotest, and TARGET. He has received research funding from Gilead and Abbvie. Pierre Nahon has received honoraria from and/or consults for Abbvie, Astra-Zeneca, Bayer, Bristol-Myers Squibb, Gilead, Ipsen and MSD. He received research grants from Abbvie and Bristol-Myers Squibb. Pietro Lampertico has served on speakers' bureau/advisory boards for BMS, Roche, Gilead Sciences, GSK, MSD, Abbvie and Janssen, Eiger, Myr pharma.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors contributed significantly to the work and reviewed the final version.

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Supplementary data

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Author names in bold designate shared co-first authorship

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nb_items=5&group_cancer=1&include_nmsc=1&include_nmsc_other=1&projection=natural-earth&color_palette=default&map_scale=quantile&map_nb_colors= 5&continent=0&rotate=%255B10%252C0%255D. Access on 06/04/2019.
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