Abstract

Obesity and the metabolic syndrome are growing epidemics associated with an increased risk for many types of cancer. In the liver, inflammatory and angiogenic changes due to insulin resistance and fatty liver disease are associated with an increased incidence of liver cancer. Regardless of underlying liver disease, cirrhosis remains the most important risk factor for hepatocellular carcinoma (HCC) although are cases of HCC arising without cirrhosis raise the possibility of a direct carcinogenesis secondary to Non-alcoholic Fatty Liver Disease (NAFLD). Moreover, metabolic syndrome and its different features may also increase the risk of HCC in the setting of chronic liver diseases of other causes such as viral hepatitis or alcohol abuse. Taking into account all these data, it is necessary to better determine the risk of developing HCC in patients with metabolic syndrome to improve the screening guidelines and develop prophylactic treatments in this setting.

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Résumé

L’obésité et le syndrome métabolique sont des affections dont la fréquence augmente et qui sont associées à plusieurs types de cancers. Dans le foie, l’inflammation et les modifications angiogéniques liées à l’insulinorésistance et à la stéatose sont associés à une augmentation de l’incidence du carcinoma hépatocellulaire. Indépendamment de la maladie causale sous-jacente, la cirrhose reste le facteur de risque principal du carcinoma hépatocellulaire (CHC) bien que des cas de CHC aient été de plus en plus fréquemment rapportés sur foie non cirrhotique, suggérant la possibilité d’une voie de carcinogénèse directe secondaire à la stéatopathie non alcoolique. En outre, le syndrome métabolique et ses différentes manifestations peuvent aussi augmenter le risque de CHC dans le contexte des maladies chroniques du foie liées à d’autres causes (hépatites virales ou alcool). Tenant compte de ces arguments, il est nécessaire maintenant de mieux évaluer le risque de CHC chez les patients avec syndrome métabolique afin d’améliorer les recommandations pour le dépistage et développer des traitements prophylactiques dans cette situation.

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Key Points

- Obesity and metabolic syndrome (MS) are growing epidemics associated with both an increased risk and worsened outcomes for many types of cancers.
- The main risk factors for HCC in the setting of Non-alcoholic steatohepatitis (NASH) are age, advanced fibrosis, diabetes mellitus, obesity and iron deposition.
- Cirrhosis remains the most important risk factor for HCC although cases of HCC may arise without cirrhosis.
- MS also increases the risk of HCC in the setting of chronic liver diseases of other causes.
- The determination of the risk of developing HCC patients with MS should improve the screening guidelines and the development of prophylactic treatments in this setting possibly independently of the presence of an underlying chronic liver damage.

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1. Introduction

The most common cause of liver disease in developed countries is Non-alcoholic Fatty Liver Disease (NAFLD) (including Non-alcoholic steatohepatitis [NASH]), a disease strongly associated with the metabolic syndrome (MS) through different mechanisms (obesity, dyslipidemia, insulin resistance, diabetes) (Fig. 1A). Unlike HCV epidemic, MS and obesity are growing epidemics in developed countries and seems to be more frequent in some ethnic groups (for example, Hispanics have the highest rate of MS in US) [1]. NAFLD comprises a spectrum of disorders from fatty liver disease to progressive inflammation and cirrhosis. In addition, increasing evidence supports that NASH can progress to hepatocellular carcinoma (HCC). It is however currently unclear whether diabetes, obesity and the MS are strong risk factors for HCC independent of the presence of NAFLD.

Fig. 1. A. Pathogenesis of non-alcoholic fatty liver diseases. B. Relation between NAFLD, NASH and hepatocellular carcinoma (HCC). Adapted from Siegel et al. [48].

2. Progression of NAFLD and NASH towards hepatocellular carcinoma

About 20 to 30% of the population has evidence of fatty liver disease attributed to NAFLD and some 10% of patients with NAFLD progress to NASH [2]. One-third to one-half of NASH patients has progressive fibrosis over 3 to 5 years and 8 to 26% of individuals with NASH may progress to cirrhosis [3]. Once cirrhosis has developed, NASH pathology may be difficult to evaluate because the fatty deposition and the inflammation often disappear. Some 40 to 60% of patients with NASH-induced cirrhosis may develop a complication of cirrhosis (including HCC) after a period of 5 to 7 years of follow-up [4,5]. Conversely, most cryptogenic cirrhosis (CC) is related to risk factors associated with NASH and the MS (obesity and diabetes) [6]. Retrospective studies suggest that as many as 4 to 27% of NASH transform to HCC after the development of cirrhosis, although the overall occurrence of HCC in the setting of NAFLD seems to be a rare complication [7] (Fig. 1B). In addition, most patients with HCC in the setting of NASH have also underlying diabetes (64%), obesity (58%) or other manifestations of the MS. Finally, longitudinal outcome studies report the prevalence HCC in NAFLD to be 0 to 0.5% and in NASH to be 0 to 2.8% over a time periods of HCC 19.5 years [8,9]. It is therefore probable that the majority of patients with MS who develop HCC also have cirrhosis before their diagnosis as shown by case reports and animal models [10].

3. May NAFLD/NASH progress to hepatocellular carcinoma in the absence of cirrhosis?

In the case reports of HCC in the setting of NASH, male patients represent the majority of cases with a mean age of 66.7 (range 45–82). These patients are older at the presentation than patients with HCC related to other chronic disease (for example patients with NASH-associated-CC are 8 years older than patients with HCV-associated cirrhosis at the time of cirrhosis and are 3 years older at the time of HCC in one study) [5,11]. Retrospective studies also support the notion that NASH accounts for a large proportion of CC (about 6.9–50% of underlying liver diseases in patients with HCC in developed countries) [12,13]. In addition, comparison of patients with CC and patients with HBV, HCV or alcohol-induced cirrhosis showed that features associated with NASH (obesity, diabetes and dyslipidemia) were all associated with CC [14,15].

Some 20% of patients with cryptogenic liver disease had evidence of NASH on liver biopsy prior to developing HCC and half of patients with CC had prior NASH or suspected NAFLD. In these series, the prevalence of HCC in the setting of CC was 6.9 to 29%. Another study showed a CC in 27% of patients with HCC and confirmed the correlation with diabetes, insulin resistance and dyslipidemia [5]. Up to 50% patients have HCC at the time of initial referral and rarely patients present with HCC in the absence of cirrhosis [16,17]. Older age and advanced fibrosis were the strongest risk factors for the development of HCC and HCC was the major cause of mortality in NASH patients with advanced fibrosis [18].
However, several case studies reported the occurrence of HCC in the setting of NASH without cirrhosis. In one recent study, HCC patients with features of MS were compared to HCC patients with overt causes or without causes (CC) who underwent surgical resection [19]. Patients with MS were older (67 years versus 59 years) and the background liver was significantly more often free of significant fibrosis (F0-F2: 65% in MS versus 26% in other group). In addition, HCC associated with MS were more often well differentiated (65% versus 28%) and some of HCC developed on a pre-existing adenoma (mainly of telangiectastic form). This observation has been more recently confirmed: NAFLD/NASH-associated HCC exhibited higher prevalence of MS compared to non-NAFLD-NASH-associated HCC. In addition, 41.7% of NAFLD-NASH-associated HCC patients have no evidence of cirrhosis. In contrast, alcohol-associated HCC also presented frequently with features of MS (73.7%) but were more frequently associated with cirrhosis (95%) [20].

4. Does serum leptin and adiponectin predict the occurrence of hepatocellular carcinoma in the setting of NASH?

Leptin levels are increased in patients with NASH [21,22]. Leptin has been shown to promote angiogenesis and mediate the progression of NASH to HCC in animal models [23]. High levels of leptin were associated with venous invasion in renal cancer, suggesting therefore a possible role of increased angiogenesis and vascular invasiveness in HCC in the setting of MS. Conversely, in patients with compensated HCV cirrhosis, insulin resistance but not serum levels of adiponectin and leptin was predictive of the occurrence of HCC [24], suggesting that the role of adipokines remains unclear in the liver carcinogenesis of patients with NASH-associated HCC.

5. Main risk factors associated with the occurrence of hepatocellular carcinoma in the setting of NASH

5.1. Obesity

The prevalence of obesity has increased to epidemic proportion over the last decades. Individuals with features of MS such as obesity may have worsened outcomes from many different types of cancer [14,25]. A meta-analysis of 11 cohort studies conducted in Europe, the US and Asia showed that those who were overweight had a significantly increased risk of developing HCC (RR: 1.07; 95% CI: 1.01–1.15) while for those who were obese, the risk was even higher (1.85; 95% CI: 1.44–2.37) [26] (Fig. 2A). Of the included studies, seven examined a total of 5037 overweight patients and 10 examined 6042 obese patients: patients who were overweight had a 17% increase in developing HCC whereas obese patients had an 89% increase in this...
risk. It was estimated that 28% of HCC cases in men and 27% in women were due to overweight or obese. In a recent population study from Sweden, 28 cases of HCC were diagnosed in 28,129 patients from 1965 to 1993 a 3-fold higher risk of HCC in obese patients [27]. Another recent European case-control study observed similarly increased risk of HCC among obese (OR 3.5 95% CI 1.3–9.2) or diabetic (OR: 3.5; CI 95%: 1.6–7.7) and the risk was even greater if both obesity and diabetes were present (OR: 11.8; CI 95%: 2.7–51.9) [28]. Compared with patients with normal BMI, the relative risk (RR) of mortality from liver cancer was 1.68 times higher in women and 4.52 times higher in men with BMI greater than 35 kg/m². Death from liver cancer among obese male patient demonstrated the highest RR of all cancers in the study [25]. This confirmed the results of another population-based study from Denmark of more than 40,000 obese patients showing that the RR of liver cancer was 1.9 compared to the general population [29]. A study from Korea examined the relationship between BMI and cancers in more than 780,000 patients followed more than 10 years [30]: again, a BMI greater than 30 kg/m² was associated with an increased risk of cancer of 26% and a RR of 1.55 was observed in obese males compared to normal controls even after controlling for HBV infection. However, these findings were not replicated in a study of Korean men with a much lower BMI (greater than 25 kg/m²) [31]. Reason for these possibly worsened outcomes remain unclear but might include associated comorbidities.

Additional arguments for the role of obesity in liver carcinogenesis are provided by surgical series. Firstly, the overall incidence of HCC in patients transplanted between 1991 and 2000 was 3.4% with a higher incidence in obese patients (4.0%) and obesity was an independent predictor for HCC in CC (OR: 11.1) and in alcoholic cirrhosis (OR: 3.2) but not in viral or autoimmune hepatitis [32]. Secondly, in patients with HCC in the setting of non-viral or alcoholic liver disease, the recurrence (more likely de novo) after curative resection was associated with an older age and high visceral fat areas (75.1% versus 43.1% at 3 years) [33]. Altogether, obesity may be definitively established as a risk factor for the development of HCC with a 1.5 to 4 times increased risk [12].

5.2. Diabetes

Large population-based studies from Sweden, Denmark and Greece demonstrated a 1.86 fold to 4-fold increase in the risk of HCC among patients with diabetes [34]. In a large longitudinal study (173,000 diabetic patients and 650,000 nondiabetic controls) followed 10 to 15 years, the incidence of HCC increased more than 2-fold among diabetic patients with even higher increase in those with longer duration of follow-up and diabetes was identified as independent risk factor for HCC [35,36].

The risk of HCC from diabetes may be decreased with the use of statins or metformin [37,38]. In the first study, 1300 cases were compared with 5200 controls. The result showed a reduced risk of HCC (between 25 and 40%) for diabetic patients under statins. The second study showed that diabetes is present in 31.2% of patients with HCC, 23.3% of cirrhotic patients and 12.7% of controls (acute hepatitis) and is an independent risk factor for HCC (OR: 2.50 in HCC group versus control and 1.46 in HCC vs liver cirrhosis in multivariate analysis). In 84% of the cases, diabetes has been present before the HCC diagnosis. Multivariate analysis showed that metformin treatment was associated with a strong reduction of the risk of HCC as compared with the use of sulphonylureas or insulin in diabetic HCC patients (OR: 0.15; CI 95% 0.04–0.50 and 0.16; CI 95% 0.06–0.46). In a recent systematic review of 13 case-control studies, 11 supported an association between diabetes and HCC with a twofold risk [39]. Diabetes remained an independent risk factor in 12 cohort studies evaluated and after adjustment for alcohol use or viral hepatitis (Fig. 2B).

In a recent study comparing 615,532 diabetic patients with 614,871 controls, the overall hazard rate for malignant neoplasm of the liver was 32.76 and was 17.41 per 10,000 patients-years, respectively for diabetic men and women. In contrast, the corresponding features for biliary tract neoplasms were much lower (1.42 and 1.60 per 10,000 patients-years). Compared with controls, diabetic patients have a 2-fold increase of malignant neoplasm (much lower when adjusting for selected clinical risk factors). For biliary tract cancer, the HR became no significant after adjustment for clinical risk factors (1.07). Diabetic patients with cirrhosis had the highest relative risk of liver neoplasm (HR: 82.25 95% CI: 76.84–94.58) while those with cholangitis had the highest risk of biliary tract neoplasm (HR 70.3; CI 95%: 51.95–95.12) [40].

6. Other risk factors of liver carcinogenesis in the setting of NASH

MS risk factors may be modified by other underlying diseases: diabetes appears to be synergistic with both virally mediated and alcohol-related HCC [41]. Steatosis also can be observed in patients with HCV infection (ranging between 31–72%), and those with both HCV and fatty liver changes have a greater risk of HCC than those with HCV alone (increased by a factor 2.81) [42,43]. In a prospective study from Taiwan, obesity led to a 4-fold increased risk of HCC in patients with HCV and diabetes led to a 2- to 3-fold increased risk of HCC regardless the underlying viral causes and had a synergistic effect with obesity leading to a > 100-fold increased cancer risk [44]. The presence of diabetes, evidenced by a positive 75 g oral glucose tolerance test, also increases the risk of HCC in patients with chronic HCV [45]. In addition, the risk of HCC increased in patients with chronic HCV in proportion to BMI with a hazard ration of 1.86 in overweight patients and of 3.10 in obese patients in comparison to underweight patients [33]. Finally, in patients with compensated HCV cirrhosis, insulin resistance predicted the occurrence of HCC [24]: the incidence of HCC was 7, 18, 27% at 5 years according to the lowest, middle and highest tertile of homeostasis model assessment (HOMA), respectively, and in multivariate analysis the HOMA index was associated with HCC occurrence (HR: 1.10; 95% CI 1.01–1.21) (Fig. 3).

In another study, the hazard ratio amongst overweight men positive for HBV surface antigen was 1.48 and it was 1.96 amongst obese men [46] and a recent retrospective study implicates iron deposition (together with diabetes) as a risk.
factor for HCC in patients with NASH-related cirrhosis [47] (Fig. 4).

7. Conclusions

Obesity and the MS are growing epidemics associated with an increased risk and worsened outcomes for many types of cancer. In the liver, inflammatory and angiogenic changes due to insulin resistance and fatty liver disease are associated with an increased incidence of liver cancer. The main risk factors for HCC in the setting of NASH are age, advanced fibrosis, cirrhosis, diabetes mellitus, obesity, iron deposition [48,49], the three latest factors being also risk factors for NASH. Regardless of underlying liver disease, cirrhosis remains the most important risk factor for HCC although are cases of HCC arising without cirrhosis raise the possibility of a direct carcinogenesis secondary to NAFLD. Moreover, MS and its different features may also increase the risk of HCC in the setting of chronic liver diseases of other causes such as viral hepatitis or alcohol abuse. Taking into account all these data, it is necessary to better determine the risk of developing HCC in patients with MS to improve the screening guidelines and develop prophylactic treatments acting on the underlying pathogenic and oncogenic mechanisms in this setting.

Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

References


