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Review

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Epidemiology of hepatocellular carcinoma in nonalcoholic fatty liver disease

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Abstract

Along with the changes in our food culture and lifestyle, conditions such as obesity, diabetes mellitus, and metabolic syndrome have been on the rise, and the incidence of nonalcoholic fatty liver disease (NAFLD), which is closely related to these diseases, has also increased rapidly. Despite being a risk factor for the development of hepatocellular carcinoma (HCC), NAFLD has no established screening method, and HCC originating from NAFLD often tends to be discovered in its advanced and symptomatic stages, which has become an important clinical problem. Even though the carcinogenicity rate among the entire population of NAFLD patients is not high compared to that of patients with viral hepatitis, since HCC also often develops from non-cirrhotic livers, it is difficult to narrow down the cases that need to be under surveillance. Going forward, it will be important to clarify the clinical characteristics and genetic background of NAFLD-related HCC and establish not only a useful surveillance method but also preventive methods.

Keywords: Hepatocellular carcinoma, nonalcoholic fatty liver disease, epidemiology

INTRODUCTION

Hepatocellular carcinoma (HCC) is the seventh most common type of cancer worldwide and the second most common cause of cancer-related death[1]. Although the majority of cases are caused by viruses such as

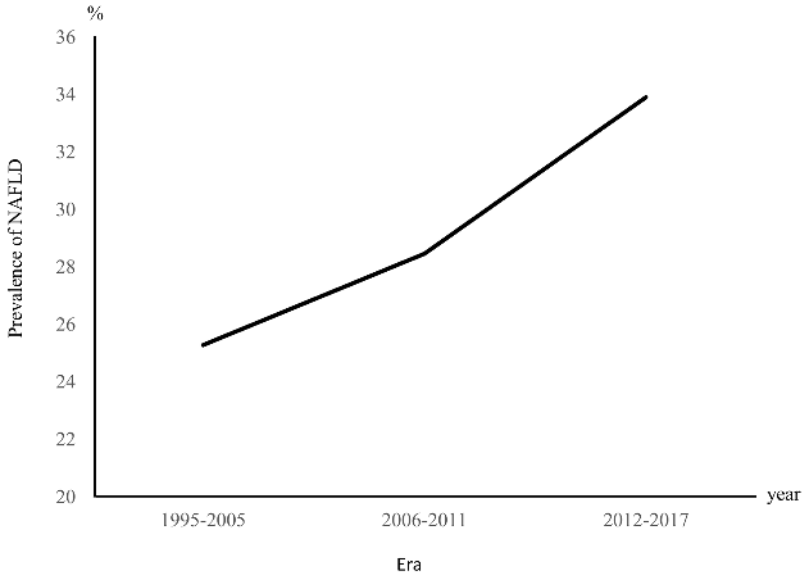

Figure 1. Trends in the prevalence of NAFLD in Asia Pacific regions. NAFLD: nonalcoholic fatty liver disease

Table 1. Global prevalence of nonalcoholic fatty liver disease

Region	Prevalence (%)
Global	24
US, middle eastern countries	30
Europe 14 countries	33
Asia-Pacific regions	
China	12.5-24.5
Japan	25
Korea	27.3
Taiwan	11.4

hepatitis B virus (HBV) and hepatitis C virus (HCV)[2,3], there has been a rapid increase in the number of cases of HCC from nonviral causes[4,5].

Although alcohol has been known to be an important nonviral cause of HCC, recent years have seen growing attention to nonalcoholic fatty liver disease (NAFLD) as an important cause of the condition[6]. The prevalence of NAFLD is closely related to the increase in the prevalence of obesity[7,8], Type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, and metabolic syndrome (MetS)[9-11] and is increasing in both developed and developing nations, with approximately 30% of the world's population being affected[12].

The prevalence of NAFLD is increasing worldwide [Table 1][13], and the trends in the Asia-Pacific region are similar [Figure 1][14]. Particularly in the developing countries, the prevalence of NAFLD has recently increased due to an increase in caloric intake and a decrease in exercise owing to the westernization of lifestyles accompanying economic development[15].

Histopathologically, NAFLD can be classified into nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver (NAFL). NASH was defined as steatosis with lobular inflammation and ballooning degeneration, with or without Mallory-Denk bodies or fibrosis. Patients with simple steatosis or steatosis with non-specific inflammation were identified as NAFL[16]. It is estimated that NASH accounts for 20%-30% of NAFLD cases, and these cases are prone to advance to severe liver fibrosis and liver cirrhosis and have been found to develop into HCC[17].

Table 2. Summary of clinical features of patients with NAFLD hepatocellular carcinoma

Incidence rate	NAFLD	Ref.[5,20-23]
	NAFLD with cirrhosis	Ref.[20,77]
	NAFLD without cirrhosis	Ref.[23,77]
	NASH	Ref.[22,77]
Age and sex	Higher incidence rate in older and male patients (compared with HCV-derived HCC)	
Complications	Obesity, type 2 diabetes mellitus, insulin resistance, cardiovascular disease, dyslipidemia, metabolic syndrome, *etc.*	
Race	Highest incidence rate in Hispanic patients, followed by Caucasian and African American patients	
Genetic elements	*PNPLA3* rs738409 SNP, *H63D* polymorphism, and *MBOAT7* rs641738 variant, *etc*.	
Other risks	Past history of drinking, iron, *etc*.	
Clinical features	Detection	Detected more often in the advanced stage and with symptoms outside of surveillance (compared with HCV-related HCC)
	Morphology	Larger tumor size, absence of encapsulation, and a more infiltrative characteristic (compared with HCV-related HCC)
	Tumor marker	Less frequently elevated AFP levels (compared with HCV-related HCC) and often elevated PIVKA-II levels
	Liver function	Relatively well preserved (compared with other etiologies)
	Background	Less advanced fibrosis (compared with HCV-related HCC)
	Prognosis	Controversial
Prevention and treatment	Metformin, exercise One promising approach; prevention of the development of fibrosis: GLP-1 receptor antagonist	

NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; PIVKA-II: prothrombin induced by vitamin K absence-II; GLP-1: glucagon like peptide-1; SNP: single-nucleotide polymorphism; AFP: alpha-fetoprotein

Although complete elimination of HBV is difficult, it has been possible to prevent the onset of cancer to some degree by suppressing the viral replication and calming the inflammation using nucleotide and nucleoside analogs[18], while the emergence of direct-acting antiviral agents has made it possible to eliminate HCV in almost all cases, thereby reducing the risk of cancer[19]. Based on these clinical advancements, the incidence of viral-related HCC, especially HCV-related HCC, is likely to continue to decrease, while the incidence of NAFLD-related HCC is likely to increase due to the lifestyle changes mentioned above[4].

This paper aims to provide a review of the literature regarding the epidemiology of NAFLD-related HCC and elucidate the problems and challenges in cases of NAFLD-related HCC that have been on the rise.

Table 2 shows a summary of the features of NAFLD HCC.

INCIDENCE OF HCC IN PATIENTS WITH NAFLD

In recent years, there have been many reports suggesting that NAFLD is an important etiology of HCC. In the US, the Surveillance, Epidemiology, and End Results reported that, between 2004 and 2009, there was a 9% annual increase in NAFLD-related HCC cases[5]. The Global HCC BRIDGE Study showed that 10%-12% of cases in North America/Europe and 1%-6% of cases in Asia diagnosed as HCC were caused by NAFLD[20]. Moreover, in Japan, the percentage of HCC patients with a nonviral etiology has increased from 10.0% in 1991 to 24.1% in 2010, which consolidates the observation that there is an increase in the number of NAFLD-related HCC cases[4].

The 130-facility cohort of the US Veterans Health Administration showed that the risk of HCC onset in NAFLD cases was 0%-38% over 5-10 years of observation, and showed that, when adjusted for the patients' race and MetS characteristics, NAFLD patients had greater annual risk of developing HCC than the controls [0.21/1000 *vs.* 0.02/1000 person-years (PYs); hazard ratio (HR): 7.62; 95% confidence interval (CI): 5.76-10.1][21]. Furthermore, the estimated annual incidence rate of HCC derived from NASH, which is an

advanced form of NAFLD, is reported to be 5.29 per 1000 person-years (95%CI: 0.75-37.56)[22], whereas the incidence rate of HCC in NAFLD patients with cirrhosis is reported to be 10.6 people per 1000 PYs[21]. In contrast, investigations in Japan revealed that approximately 32% of NAFLD-related HCC cases did not have cirrhosis, which may be a characteristic of NAFLD-related HCC[23].

CLINICAL FEATURES OF NAFLD-RELATED HCC

Unlike other etiologies, NAFLD-HCC is generally characterized by a large tumor size, moderately to highly differentiated histology, and absence of encapsulation[24] and is often discovered in the advanced stages of the disease[5,25]. Furthermore, NAFLD-related HCC is more infiltrative than HCV-related HCC, and often tends to be detected outside of surveillance[26].

There have been reports comparing HCV-related HCC and NASH-related HCC that have shown NASH-related HCC occurs at older age than HCV-related HCC[27], and the prevalence of obesity, T2DM, and dyslipidemia is greater in NASH-related HCC[28]. Furthermore, although an elevated alpha-fetoprotein (AFP) level is observed in 69.6% of HCV-related HCC patients[29], this occurs in < 1/3 of NASH-related HCC patients[28], and an elevated prothrombin induced by vitamin K absence-II (PIVKA-II) level is relatively common in NAFLD-related HCC patients[30].

Strategies have been provided to treat HCC, regardless of its etiology[31], and there have been various reports related to the treatment results and prognosis. It has been reported that the percentage of patients who were able to receive curative treatments such as liver resection, including liver transplant, was lower for NAFLD-related HCC than HCV-related HCC (NAFLD-related HCC: 21/212 *vs.* HCV-related HCC: 80/275)[27] and other etiologies of HCC[32]. In contrast, NAFLD-related HCC patients had a low cirrhosis prevalence, liver functions such as the synthetic capacity were relatively well preserved[32,33], and liver resection rates were higher than those of HCV-related HCC[26,33]. However, as NAFLD-related HCC occurred at an advanced age and patients often had cardiovascular and metabolic complications, there was no difference in the overall survival rate between NAFLD-related HCC (one year: 56%; three years: 23%) and HCV-related HCC (one year: 58%; three years: 21%)[27]. In some reports, the overall survival of NAFLD-related HCC patients was lower than that of HCV-related HCC patients[29,32]. Conversely, there are reports suggesting that the relapse-free survival rate was high after curative resection of NAFLD-related HCC[34] and that the overall survival was nearly the same or greater than that for HCV-related HCC or alcoholic cirrhosis-related HCC[35,36], thus a consensus has not been obtained.

Link to obesity and T2DM

NAFLD is strongly related to insulin resistance, MetS, and cardiovascular disease[9-11]. In the UK, it was reported that the increase in cancer incidence and cases attributed to NAFLD occur in parallel with the steady increase in MetS incidence observed among HCC patients[25]. In particular, T2DM and obesity are closely related to NAFLD/NASH, and there are concerns that HCC will increase in the future[37].

It has been reported that up to 70% of T2DM patients and up to 90% of patients with obesity have NAFLD[37,38]. Furthermore, a high percentage of patients with T2DM and obesity have advanced fibrosis[39-43]. The emergence of T2DM occurs in parallel with fibrosis, and the increase or decrease in body mass index (BMI) over time is related to the progression or improvement of liver fibrosis in NAFLD patients[39-41,43].

Obesity

Obesity has been increasing globally for the past several decades along with the changes in the food and lifestyle culture. HCC has been increasing among patients with obesity, and a perspective study involving a US population showed that the relative risk (RR) of death in patients with obesity grade II and I is 4.52 and

1.90, respectively[35]. There have been other reports linking HCC and obesity. In a prospective cohort study in Europe, general obesity (RR: 2.19) and abdominal obesity (RR: 2.03) were reported to be related to the risk of HCC[44]. Compared to the normal body weight, the RR of HCC was 1.17 (95%CI: 1.02-1.34) in those who are overweight and 1.89 (95%CI: 1.51-2.36) in those who are obese[45].

In terms of the relationship between BMI and HCC, a study cohort in Italy showed that the RR of HCC onset for BMI > 30 kg/m^2 was 1.97 times higher[46]. Studies in South Korea showed that it was 1.56 times higher for BMI > 30 kg/m^2[47]. Other studies showed, as mentioned above, that it was 1.13 for BMI of 25-29.9 kg/m^2 and increased to 4.52 for BMI between 35 and 39.9 kg/m^2[35]. Furthermore, a meta-analysis of 11 cohort studies showed that an increase in BMI by 5 kg/m^2 increases the risk of HCC by 24%[45]. Furthermore, the European Prospective Investigation into Cancer reported that the waist-hip ratio and a rough estimate of abdominal fat are good prognostic factors of HCC[44] and suggests that the assessment of fat deposition is just as important as assessing BMI. It was also reported that obesity during early adulthood is a risk factor of HCC and that the increase in BMI during early adulthood speeds up the onset of HCC[48].

T2DM

HCC has been increasing among T2DM patients[49,50]. An epidemiological study in the US on the RR of HCC in T2DM patients showed that the risk of HCC increased by 2.87 times (95%CI: 2.49-3.30) due to T2DM[51]. A multicenter case-control study in Italy reported that the risk of HCC due to T2DM had an odds ratio of 4.33 (95%CI: 1.89-9.86)[36]. Furthermore, examination of non-HCV HCC cases showed that the risk of HCC in T2DM patients is twice as high[52], and the risk of developing HCC due to T2DM when there is no liver cirrhosis is 1.353 times higher (95%CI: 1.249-1.465)[53], whereas a history of T2DM is also a risk factor (HR: 2.14, 95%CI: 1.69-2.71)[54]. Furthermore, a meta-analysis showed that HCC prevalence and incidence rates increase by 2.5 times due to T2DM[55].

T2DM is mediated by insulin resistance, and the subsequent inflammatory cascade is thought to be involved in the progression of the condition to NAFLD and HCC[55-58]. With respect to the relationship between NAFLD-related HCC and T2DM, it was reported that, while the prevalence of T2DM in HCV-related HCC patients was 24.9%, the prevalence was 73.1% in NAFLD-related HCC patients, which suggests a strong relationship between the two[59].

Age and sex

Incident rate of HCC is high in men regardless of etiology including NAFLD[60]. A study in the US suggests that the incidence rate of HCC is higher in men than in women (0.22 *vs.* 0.04 per 1000 PYs), whereas the incidence rate of HCC in NAFLD patients was found to be higher in patients aged ≥ 65 years than in younger patients [0.41 *vs.* 0.01 (< 45 years) and 0.02 (45-64 years) per 1000 PYs][21]. As mentioned above, BMI is related to the onset of HCC, and, although UK studies have shown a positive correlation between BMI and HCC (HR: 1.19, 99%CI: 1.12-1.27), this relationship was reportedly more profound in men, in whom the risk of HCC increases linearly from a BMI of > 22 kg/m^2[61]. The severity of NAFLD and the level of progression of fibrosis are risk factors of HCC development. In the young, NASH is more prominent in males, while, in older patients (> 50 years), it is more common in women and the severity of NASH is higher in women as well[60,62]. Furthermore, a cross-sectional study on NAFLD reported that increasing age is correlated with the severity of fibrosis in NASH patients[63-65].

Race and genetic elements

Although it has been reported that there is no difference in the extent of liver damage between Hispanic and Caucasian patients with NAFLD[66,67], the incidence of HCC was highest in Hispanic patients (0.29 per 1000 PYs), followed by Caucasian patients (0.21 per 1000 PYs) and African American patients (0.12 per 1000

PYs)[21]. However, US-born Hispanic patients had higher HCC incidence rates than Hispanic patients born outside of the US[68], which suggests the importance of other risk factors such as the environment, lifestyle habits, and MetS, in addition to polymorphism of the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) gene.

PNPLA3 rs738409 single-nucleotide polymorphism, which is a risk factor of steatosis, NASH, and fibrosis[69], is also a risk factor of HCC (odds ratio: 1.40)[70]. Furthermore, the risk allele "G" is observed in 40% of the European population, and it reportedly increases the risk of HCC by approximately 12 times[71]. In HCC patients, GG homozygosity is related to early onset (at young age), background liver disease with short cirrhotic history or less fibrosis, diffuse-type HCC, and poor prognosis[71].

In addition, it has been reported that the *H63D* gene, which is a common polymorphism of human hereditary hemochromatosis, is related to the risk of non-cirrhotic HCC incidence in Africans[72], whereas the membrane-bound O-acyltransferase (*MBOAT7*) rs641738 variant is reportedly related to NAFLD-related HCC with non-advanced fibrosis[73].

Others

Previous alcohol intake and iron level in hepatocytes have been reported as risk factors of HCC in NASH patients[74,75], with the increase in hepatocellular iron levels being related to advanced fibrosis in NAFLD[76]. A study in Italy compared 51 NASH cirrhosis-related HCC patients against 102 patients without HCC and found that hepatocytes staining positive to iron were in significantly greater quantity in the HCC cohort than in the non-HCC cohort[75].

HCC in NAFLD with cirrhosis

As mentioned above, a study that examined 296,707 NAFLD patients showed that 490 patients developed HCC (0.21 per 1000 PYs), and the incidence rate of HCC was significantly higher than that of the control group (0.02 per 1000 PYs, HR: 7.62, 95%CI: 5.76-10.09). Among the NAFLD patients, those with cirrhosis had the highest annual incidence rate of HCC (10.6 per 1000 PYs), and 1.6-23.7 people per 1000 PYs were at risk[21]. In another report, the incidence of NAFLD patients with cirrhosis who developed HCC was from 2.4% at seven years to 12.8% over three years[77], which was marginally lower than the 4% annual incidence of cancer observed in cases of cirrhosis caused by HCV[22,77].

With respect to the relationship between the indicators of fibrosis and development of cancer from NAFLD, patients with a cirrhosis diagnosis and a high Fibrosis-4 (FIB-4) score had the greatest risk of HCC (13.5 per 1000 PYs), whereas patients without a cirrhosis diagnosis and a low FIB-4 score had a low risk of HCC development (0.04 per 1000 PYs)[21]. A separate study showed that a high NAFLD fibrosis score and a high FIB-4 score were strongly related to the incidence of HCC[78]. Furthermore, sex (male), age (≥ 70 years), T2DM, and high blood pressure have been reported as risk factors of HCC in NAFLD patients with cirrhosis[30].

Relationship between cryptogenic cirrhosis and NAFLD

Liver cirrhosis is the most common cause of HCC, and 80%-90% of HCC patients have had cirrhosis[79]. Although viruses are common origins of liver cirrhosis, it has been reported that, in 6.9%-50% of HCC cases, the etiology of liver disease could not be determined[80-82]. A prospective US study[82] showed that cryptogenic cirrhosis (CC) is responsible for up to 29% of the etiology of HCC. Half of these patients had histological and clinical features of NAFLD, and another retrospective study showed that HCC patients with CC had a greater prevalence of T2DM and obesity than those who developed the condition from a virus or alcoholic cirrhosis[83]. Given its similarity to NASH cirrhosis, a strong correlation between CC

and NAFLD was suggested, and many of the CC cases were severely advanced NASH, that is, burned-out NASH[83-86].

Based on the abovementioned data, it is speculated that the role of NAFLD in HCC etiology is greater than the data that have been reported, and the existence of burned-out NASH is a point to be noted in epidemiological research related to NAFLD-related HCC.

HCC in NAFLD without cirrhosis

Several cross-sectional studies showed that 15%-50% of patients diagnosed with HCC without cirrhosis were patients with non-cirrhotic NAFLD[35,87-89]. This suggests the possibility that NAFLD is an independent risk factor of HCC, even in those cases without cirrhosis[82,90,91].

There has been an increase in the number of cases of HCC that developed in NAFLD patients without cirrhosis[92,93]. The characteristics of NAFLD-related HCC without cirrhosis include a larger tumor size[94-96], older age, and slightly lower prevalence of T2DM than those of NAFLD-related HCC patients with cirrhosis[94]. In a recent meta-analysis of a cohort of NAFLD patients without cirrhosis, the cumulative HCC mortality for the study periods of up to 20 years was between 0% and 3%[77].

In the cohort study mentioned above, approximately 20% of NAFLD-related HCC patients did not have cirrhosis[21], and NAFLD patients without cirrhosis had an annual HCC incidence of 0.08 per 1000 PYs (*vs.* 0.02 per 1000 PYs in the control group without NAFLD), whereas reports from Japan also suggested that approximately 32%[22] to 49% (28% being in stages 1-2 of fibrosis)[30] of NAFLD-related HCC cases had no cirrhosis. A separate study reported that 10%-75% of NAFLD-related HCC patients had no cirrhosis in their background[87,89,97], suggesting that NASH itself can promote the development of HCC and that HCC can develop from NASH and simple steatosis without fibrosis[33].

As a mechanism of how HCC develops in NAFLD patients without cirrhosis, the possibility of transformation of hepatocellular adenoma (HCA) comes to mind. NAFLD is strongly correlated to obesity, MetS, and T2DM, among others[30]. Furthermore, it has also been reported that there is a relationship between the prevalence of obesity/MetS and HCA (particularly related to the subtype that has a risk of malignant transformation: inflammatory HCA)[98,99], which seems to support this possibility. Furthermore, as a result of a recent study, some of the cases of HCC developing in NAFLD patients show steatosis, ballooning, Mallory bodies, and pericellular fibrosis in its histological presentation, and there is also a characteristic subtype called steatohepatitic HCC that resembles steatohepatitis[100], which suggests that there is a close relationship between non-cirrhotic NAFLD and development of HCC.

CLINICAL ISSUES AND CHALLENGES IN HCC SURVEILLANCE OF NAFLD PATIENTS

With the increase in NAFLD prevalence, there has been an increase in the prevalence of NAFLD-related HCC, albeit not as high as that of viral-related HCC, which has led to the increasing importance of surveillance.

Even though the AASLD (American Association for the Study of Liver Diseases) and EASL-EORTC (The European Association for the Study of the Liver-The European Organisation for Research and Treatment of Cancer) Guidelines recommend patients with cirrhosis to be screened for HCC every six months[101], HCC surveillance of NAFLD-cirrhosis cases is included under “Other conditions” in the AASLD Guidelines[102], and there are no specific recommendations. In general, screening is performed using ultrasound examinations, but there are limitations of using this approach for patients with obesity[103,104]. Although magnetic resonance imaging scans provide excellent lesion detectability, it is difficult to recommend this approach for screening due to its high cost and availability issues.

In contrast, since the carcinogenic risk is not high in non-cirrhotic NAFLD, and because only 23% of all NAFLD-related HCC cases are detected by screening and 62.3% of cases are found already symptomatic[25], the cost-effectiveness of HCC surveillance for non-cirrhotic NAFLD is poor. Furthermore, it is not at a level to be recommended. For this reason, tools and biomarkers that help to narrow down high-risk populations of cancer development is important for HCC surveillance among patients with non-cirrhotic NAFLD.

The problem of HCC surveillance in NAFLD patients is to narrow down those patients who should be screened. The most important approach would be to distinguish whether the patient exhibits severe fibrosis and cirrhosis, which indicate a risk of HCC development. The gold standard for the diagnosis of fibrosis is liver biopsy, but it involves the issue of invasiveness, and, in recent years, the problem of sampling error has also been reported. To narrow down severe fibrosis populations, the use of the aspartate aminotransferase-to-platelet ratio index (APRI)[105], NAFLD fibrosis score[106], and FIB-4 index[107] have been reported as a simple approach. There are also reports related to the usefulness of special ultrasound tests such as Fibroscan[108].

In recent years, it has been reported that a scoring system based on age, sex, T2DM or viral hepatitis history, aminotransferase, and AFP is useful regardless of the etiology of the condition[109], and we may need to consider whether it can be introduced in the surveillance of NAFLD patients.

Furthermore, in view of the differences observed between races, it may be useful to actively screen more Hispanic populations, who are at a high risk of developing NAFLD-related HCC. Additionally, although it may be useful to use *PNPLA3* rs738409 polymorphism for screening from a genetic point of view, it would be difficult to introduce this approach to the surveillance procedures at this stage, when we take into consideration the cost[110].

On the other hand, while HCC is often detected using ultrasound and AFP tests, the frequency of high AFP levels in NAFLD-related HCC cases is not as high as that in HCV-related HCC cases, and there are also reports suggesting that there are many cases with high PIVKA-II levels. As such, it may be one approach to introduce the evaluation of PIVKA-II levels to the surveillance process.

PREVENTION AND TREATMENT

At present, it is important to prevent progression of NAFLD as early as possible by improving lifestyle; this prevents the development of NAFLD-related HCC. It has also been reported that exercise has a preventive effect on the development of HCC[111,112] and that exercising for ≥ 5 days per week reduces the RR of HCC to 0.56[113]. Conversely, certain recent reports have suggested the possibility of therapy with drugs such as GLP-1 receptor antagonists and metformin.

GLP-1 receptor antagonist

Fibrosis is a risk factor of cancer, and one target should be to prevent the development of fibrosis. The use of drugs targeting dyslipidemia, insulin resistance, oxidative stress, inflammatory cytokines, apoptosis, and the angiotensin pathway, among others, has been explored[114], but, until now, no definite drug therapy has been established. However, reports from a phase 2 trial suggest that glucagon-like peptide-1 (GLP-1) receptor antagonists may prevent the occurrence of HCC by ameliorating liver fibrosis in NAFLD patients[115]. Phase 3 trials are expected to be conducted in the future.

Metformin

The use of metformin is related to the decrease in HCC incidence in T2DM patients[116-121], and a meta-analysis showed that the use of metformin in T2DM patients reduced the risk of HCC by 70%[122] or

50%[119]. The mechanism of this action is reportedly via AMP-activated protein kinase activation[123] and mammalian target of rapamycin inhibition[124]. It has also been reported in prospective studies that the use of metformin in patients with cirrhosis increased survival[125] and that it improved the outcome of radiofrequency ablation treatments given to HCC patients[126]. On the other hand, insulin and sulfonyl preparations have been shown to increase the risk of HCC[127,128].

CONCLUSION

There has been a dramatic increase in the number of NAFLD patients, which is closely related to obesity, T2DM, and MetS, as our food and lifestyle habits change. Although the risk of HCC development is not as high as that due to viral hepatitis, because of the large population of patients with NAFLD, there has been an increase in HCC developing from NAFLD. NAFLD-related HCC is often discovered in its advanced stages, and, due to problems of low detectability by ultrasound examinations due to patients being obese and the development of the condition in non-cirrhotic livers, there is yet to be an effective method of surveillance. At present, there are no epidemiological data that can help overcome these challenges. In the future, there will be a need for studies focusing particularly on HCC surveillance in non-cirrhotic NAFLD. Immediate efforts toward early detection and improvement of treatment of NAFLD-related HCC will be important, such as enlightenment of and cooperation with medical professionals working on patients with obesity, T2DM, MetS, and cardiovascular disease, in addition to educational activities for NAFLD patients. Moreover, as weight gain during early adulthood is a risk factor of HCC, it is important to raise awareness of this matter through school education. On the other hand, regarding medical treatment, there are currently no therapeutic drugs that have been shown to be effective; however, some drugs have promise. Metformin is associated with a decrease in the incidence of HCC in T2DM, which is closely related to NAFLD. Furthermore, a phase 2 trial has provided evidence that GLP-1 receptor antagonists ameliorate liver fibrosis, which is considered to predispose individuals with NAFLD to developing HCC. The efficacy of GLP-1 receptor antagonists will be determined in phase 3 trials.

DECLARATIONS

Authors' contributions

Study concept and design, literature search, drafting of the manuscript: Moriguchi M, Seko Y, Takahashi A
Supervision of the project: Itoh Y

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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