Check for updates

Liver International Communications

WILEY

Liver INTERNATIONAL COMMUNICATIONS

ORIGINAL ARTICLE OPEN ACCESS

Dynamic Changes in Metabolic Syndrome and Risk of Hepatocellular Carcinoma: Evidence From a Nationwide Japanese Cohort

Yutaka Yata[1,2,3] | Naoki Kimoto[4] | Yohei Miyashita[5] | Takeshi Aketa[6] | Takashi Washio[7] | Kosuke Onoue[8] | Masami Yabumoto[2] | Sawako Uchida-Kobayashi[3] | Norifumi Kawada[1,3] | Masafumi Kitakaze[2,9]

[1]Department of Gastroenterology, Hanwa Memorial Hospital, Osaka, Japan | [2]Department of Medical Research and Development, Hanwa Memorial Hospital, Osaka, Japan | [3]Endowed Department of Liver Cancer Treatment, Osaka Metropolitan University, Osaka, Japan | [4]Graduate School of Biosciences, Osaka University, Osaka, Japan | [5]Department of Cardiovascular Medicine, Graduate School of Medicine, Osaka University, Osaka, Japan | [6]Asclepius Corporation, Osaka, Japan | [7]Institute of Scientific and Industrial Research, Osaka University, Osaka, Japan | [8]Nonprofit Organization (NPO) A Scientific Approach to Medicine, Osaka, Japan | [9]The Osaka Medical Research Foundation for Intractable Diseases, Osaka, Japan

Correspondence: Masafumi Kitakaze (kitakaze.masafumi@kinshukai.or.jp)

Received: 20 April 2026 | **Revised:** 12 August 2026 | **Accepted:** 18 September 2026

Keywords: big data | early-stage metabolic syndrome | hepatocellular carcinoma | metabolic syndrome | prevention of metabolic syndrome | temporal dynamic changes

ABSTRACT

Aim: Metabolic syndrome (MetS) is a known risk factor for hepatocellular carcinoma (HCC), but the impact of cumulative MetS burden and changes in MetS status over time remains unclear. This study aimed to assess these associations using a large-scale Japanese health dataset.

Methods: We analysed medical data from 2.71 million Japanese individuals collected between 2005 and 2020. The study evaluated the incidence of HCC in relation to MetS, preMetS (an early stage of MetS), and five MetS components: triglycerides ≥ 150 mg/dL, HDL-C < 40 mg/dL in men or < 50 mg/dL in women, fasting blood glucose ≥ 100 mg/dL, blood pressure ≥ 130/85 mmHg, and waist circumference ≥ 90 cm in men or ≥ 80 cm in women. For the dynamic analysis, participants were classified into four groups based on MetS status during two predefined periods, 2010–2011 and 2012–2013: MetS-free, MetS-developed, MetS-persistent, and MetS-recovered. As Type 2 diabetes (T2D) is an extreme metabolic state and a strong independent risk factor for HCC, this study assessed the impact of MetS on HCC risk excluding T2D.

Results: Among the 2.71 million individuals, 63 435 developed HCC. Compared with the non-MetS group, both the MetS group (HR 1.42, 95% CI 1.39–1.45) and the preMetS group (HR 1.26, 95% CI 1.22–1.29) had significantly increased HCC risk. A higher number of MetS components was associated with progressively increased HCC incidence. Individuals who developed or maintained MetS over time had a higher risk of HCC than MetS-free individuals, whereas those who recovered from MetS had a reduced risk.

Conclusion: MetS and even preMetS are significant risk factors for HCC. Importantly, improvement in MetS status may help prevent HCC. These findings suggest that early identification and management of MetS could play a key role in liver cancer prevention.

Abbreviations: BMI, body mass index; BP, blood pressure; FBS, fasting blood glucose; HCC, hepatocellular carcinoma; HDL-C, high-density lipoprotein cholesterol; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MetS, Metabolic syndrome; T2D, Type 2 diabetes; TG, triglycerides.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2026 The Author(s). *Liver International Communications* Published by John Wiley & Sons Ltd

Lay Summary

MetS is a common health condition that increases the risk of HCC. In this nationwide study of more than 2.7 million people in Japan, persistent MetS was associated with the highest risk of HCC, whereas improvement in MetS was associated with a lower risk. These findings suggest that early detection and effective management of MetS may help prevent HCC.

1 | Introduction

Metabolic syndrome (MetS) characterized by factors such as hypertension, hyperglycemia, obesity, and abnormal levels of cholesterol and triglycerides is strongly linked to the incidence of cardiovascular disease, stroke, Type 2 diabetes (T2D), and carcinogenesis. In the liver, hepatocellular carcinoma (HCC) arising from MetS, fatty liver, and metabolic dysfunction-associated steatohepatitis (MASH) has been increasing year by year [1, 2]. We have previously reported that MetS is associated with an elevated risk of pancreatic carcinogenesis compared to non-MetS individuals [3], although the mechanisms by which MetS contributes to HCC are complex and involve multiple synergistic and interacting factors [4]. On the other hand, the depth and dynamic changes in MetS are not well elucidated despite its importance considering the prevention of HCC: there is currently no conclusive evidence that the early-stage MetS (preMetS) is associated with HCC development, and, the contribution of dynamic changes in MetS, i.e., the progression or regression of MetS is not elucidated well although this issue is important considering the prevention of HCC.

Therefore, to clarify the precise and dynamic relationship between MetS and HCC, we conducted a retrospective observational study using a large-scale Japanese health database to examine MetS status, longitudinal changes in its components, and the incidence of HCC over a 10-year period. We also investigated whether preMetS was associated with an increased risk of HCC.

2 | Subjects and Methods

As of 2005, a total of 2712570 Japanese individuals were registered, and their physical findings, laboratory test results, and disease status under the national health insurance system were tracked for more than 10 years. At the time of enrollment, data on prescription medications were also obtained. After assessing the presence or absence of MetS, participants were followed regardless of their MetS status to evaluate the incidence of HCC. MetS was defined according to the modified criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATPIII).

2.1 | Study Design

This study was a retrospective observational study conducted in accordance with the principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

2.2 | Participants

The analysis was based on health insurance claims data obtained from the Japan Medical Data Center (JMDC), a leading company in Japan that compiles large-scale medical databases. The study included 2712570 insured individuals from 2005 to 2020. The database comprises standardized eligibility and claims data provided by health insurance societies, including information on employees of general companies and their family members, as well as comprehensive records of all treatments received by insured individuals at all medical facilities and procedures conducted on specific patients. For the analysis, all personal data were anonymized using non-linkable anonymization techniques to ensure confidentiality. Because detailed virological data, including serological markers such as HBsAg, anti-HBc, and anti-HCV, were not uniformly available in the JMDC database, direct assessment of the interaction between MetS and chronic viral hepatitis was not feasible in the present study. To reduce confounding as much as possible, individuals with clearly documented viral liver disease were excluded based on International Classification of Diseases, 10th Revision (ICD-10) diagnostic codes, and all multivariable analyses were adjusted for age, sex, and smoking status. Because this was an insurance claims-based observational study, residual confounding and surveillance bias could not be completely eliminated and were considered when interpreting the findings.

2.3 | Ethics

The study protocol was approved by the Ethics Committee of the Evidence Founder Club, Osaka, Japan (approval no. EU20210515-1), which is independent of JMDC and the study sponsors. Because this was a retrospective observational study using anonymized data, the requirement for informed consent was waived in accordance with the Japanese ethical guidelines. Instead, JMDC disclosed the study information through an opt-out procedure.

2.4 | Definition of MetS

MetS was defined based on the modified criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATPIII) [5], as the presence of three or more of the following components: (1) serum triglycerides (TG) $\geq$ 150 mg/dL; (2) high-density lipoprotein (HDL) cholesterol $<$ 40 mg/dL in men or $<$ 50 mg/dL in women; (3) fasting blood glucose $\geq$ 100 mg/dL; (4) blood pressure (BP) $\geq$ 130/85 mmHg; and (5) waist circumference $\geq$ 90 cm in men or $\geq$ 80 cm in women. The condition of preMetS was defined as the presence of one or two of the above components. Individuals who did not meet the criteria for either MetS or preMetS were classified as the non-MetS group. Participants with T2D were excluded from the analysis. Since T2D represents an advanced metabolic disorder and a strong independent risk factor for HCC, which could obscure

29941393, 2026, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lci2.70057, Wiley Online Library on [05/10/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

the specific contribution of MetS and pre-MetS to hepatocarcinogenesis. Accordingly, by excluding T2D, the study was designed to more clearly delineate the independent role of MetS-related metabolic abnormalities at the prediabetic stage and to more accurately evaluate the association between dynamic changes in MetS status and HCC risk. In this study, BMI was not used to define MetS or as a surrogate for waist circumference. Instead, BMI was analysed separately as an independent predictor to evaluate its association with HCC risk beyond the MetS definition.

2.5 | The Study Protocol

Clinical data were obtained and recorded from all enrolled participants prior to the examination and identification of patients diagnosed with HCC according to the ICD-10, coded as C22.0. First of all, since BMI among the components of MetS is critically important, we investigated the relationship between the values of BMI and the incidence of HCC. Secondly, the incidence of HCC was compared between cohorts with and without MetS using Kaplan–Meier estimates over a 40.7-month observation period. The study period (2010–2020) represents the overall observation period of the database, whereas the mean follow-up duration of 40.7 months reflects the average follow-up from baseline to HCC diagnosis or censoring. Because participants joined the cohort at different times, the follow-up periods varied.

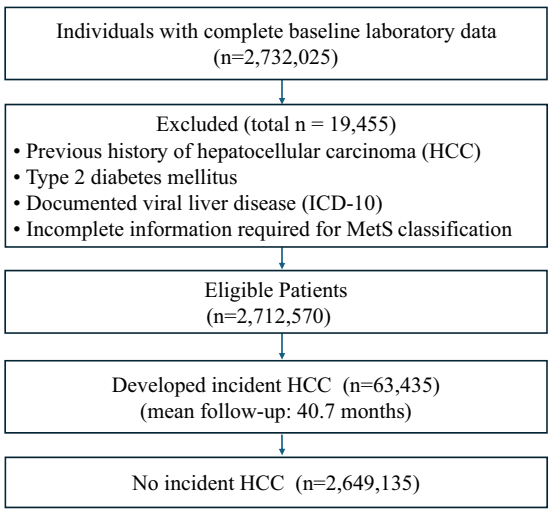
A total of 2 732 025 individuals had complete baseline blood test data. Ultimately, a cohort of 2 712 570 individuals without a prior history of HCC and with complete data necessary to determine the presence of MetS and its major components was identified (Figure 1), and these subjects were followed during each observation period. The Cox proportional hazards model was also used to calculate hazard ratios (HRs) between groups with 0 to 5 MetS components, as defined by the NCEP/ATPIII criteria [5].

Thirdly, to investigate the impact of metabolic dynamics over time on the development of HCC, a sub-analysis was conducted by enrolling 206 847 participants whose metabolic status was reliably tracked during both 2010–2011 (from January 2010 to December 2011) and 2012–2013 (from January 2012 to December 2013). The dynamic analysis included only participants who underwent health examinations in both 2010–2011 and 2012–2013 and had sufficient data to determine MetS status at both time points. Consequently, the sample size was substantially reduced from the main cohort ($N = 2\,712\,570$) to the dynamic subcohort ($N = 206\,847$).

These individuals were classified into four groups based on the presence or absence of MetS during two periods: (1) 2010–2011 and (2) 2012–2013. Specifically, among those with MetS in 2010–2011, individuals were further categorized based on whether MetS persisted or improved by 2012–2013. Those who recovered from MetS ($n = 10\,034$) and those with persistent MetS ($n = 13\,595$) were tracked until the end of the observation period or the onset of HCC. Similarly, individuals without MetS in 2010–2011 were categorized into the MetS-developed group ($n = 11\,248$) or the MetS-free group ($n = 171\,970$), depending on whether MetS appeared by 2012–2013 or not, and were followed in the same manner. Additionally, to verify the causal relationship between MetS and HCC, a sub-analysis was performed excluding participants who developed HCC within 3 years after entry.

2.6 | Statistical Analysis

In the primary analysis, time-to-event data were evaluated using Kaplan–Meier estimates and compared using the log-rank test. The entry time for the Kaplan–Meier plot, i.e., time = 0, was variable. Censoring occurred when participants died or became lost to follow-up. For missing data, a complete case analysis (listwise deletion) was employed, and no sensitivity analyses were performed. HRs were estimated using the Cox proportional hazards



Input variable: Blood test value at the initial medical examination criteria for pathology: ICD10 sub-classification code (2013) includes a record of HCC (C22.0) in the receipt record during the observation period.

FIGURE 1 | Flow diagram of participant selection. A total of 2 732 025 individuals had complete baseline laboratory data. After excluding participants with prevalent HCC, T2D, documented viral liver disease, or incomplete information required for MetS classification, 2 712 570 eligible individuals were included in the final analysis. The analyses were adjusted for age, sex, and smoking status. Incident HCC was identified using ICD-10 code C22.0 recorded during follow-up. During a mean follow-up of 40.7 months, 63 435 participants developed HCC.

29941393, 2026, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lci2.70057, Wiley Online Library on [05/10/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

model based on MetS group assignment, including combinations of MetS and non-MetS groups and their respective components. *p*-values for hypothesis testing between groups were also calculated. The model was adjusted for smoking status, age, and sex, as these factors are known to influence the incidence of HCC. Age was treated as a continuous variable in the Cox proportional hazards model. To assess the assumption of log-linearity, a score test was performed based on scaled Schoenfeld residuals, including scatter plots with survival time on the horizontal axis. No strong evidence was found to suggest a violation of the log-linearity assumption for any of the covariates, based on the scaled Schoenfeld residuals plotted on the vertical axis. The likelihood ratio test of the regression coefficients for interaction terms revealed a significant interaction between sex and age, while interactions among other covariates (e.g., smoking) were not significant. Therefore, a model including an interaction term between sex and age was employed. Sensitivity analyses were performed by excluding participants who developed HCC within 3 years after study entry to reduce the possibility of reverse causation. In addition, analyses using ICD-10 code C22.0 for HCC identification were conducted to confirm the robustness of the primary findings. All statistical analyses were conducted using Python v3.10 and relevant packages, including Lifelines v0.27.8 (https://github.com/nkimoto/PKMetS).

2.7 | Role of the Funding Source

The study sponsor was not involved in the study design, data collection, analysis, interpretation, manuscript preparation, or the decision to submit the study for publication.

3 | Results

Among the 2 712 570 registered participants, 63 435 developed HCC during a mean follow-up period of 40.7 months (Figure 1). The clinical characteristics of the participants are summarized in Table 1. Table 1 also indicates that the preMetS group showed intermediate clinical characteristics between the non-MetS and MetS groups, whereas the MetS group had the greatest burden of metabolic abnormalities, supporting the graded increase in HCC risk observed in the subsequent analyses. In the analysis of BMI and HCC, a U-shaped curve was observed, with a BMI of 21 representing the nadir. Both low and high BMI values were associated with higher HRs compared to the midpoint (Figure 2). Stratified analysis by sex showed a similar U-shaped association in both men and women, with elevated HRs at both extremes of BMI. However, the trend of increased risk with higher BMI was more pronounced in men, suggesting that men with elevated BMI are at greater risk of developing HCC.

In the analysis of the number of MetS components and the incidence of HCC, the cumulative incidence of HCC increased significantly as the number of MetS components increased ($p < 0.05$) (Figure 3). The HR for HCC also increased progressively with the number of MetS components, from 1 to 5 (HRs: 1.15, 1.37, 1.59, 1.77, and 1.92; all $p < 0.05$). These findings indicate that the accumulation of MetS components has a detrimental effect on the development of HCC.

Analysis of temporal dynamic changes in MetS and incident HCC revealed significant differences in cumulative HCC

TABLE 1 | Characteristics of 2 712 570 participants with complete data for identifying metabolic syndrome (MetS) and major risk factors.

The parameters for the diagnosis of MetS and important risk factors	All data (*N* = 2 712 570)	NCEP/ATPI criteria of MetS		*t*-test
		Non-MetS (*N* = 2 380 777)	MetS (*N* = 331 793)	
Age, median age	54 (47–62)	53 (46–61)	59 (52–66)	< 0.001
Women, *n* (%)	1 136 983 (41.9%)	1 042 507 (43.7%)	94 476 (28.4%)	< 0.001
Smoker, *n* (%)	675 448 (24.9%)	570 806 (23.9%)	104 642 (31.5%)	< 0.001
BMI, median BMI	22.5 (20.3–25.0)	22.0 (20.0–24.2)	27.0 (24.8–29.5)	< 0.001
Abd circumference, median cm	80.5 (74.0–87.2)	79.0 (73.0–85.0)	93.0 (88.0–98.5)	< 0.001
sBP, median mmHg	118 (108–129)	116 (106–126)	134 (126–143)	< 0.001
dBP, median mmHg	73 (65–82)	72 (64–80)	85 (78–91)	< 0.001
HbA1c, median %	5.4 (5.2–5.7)	5.4 (5.2–5.6)	5.8 (5.5–6.2)	< 0.001
Fasting glucose, medain mg/dl	92 (86–99)	91 (85–97)	105 (99–117)	< 0.001
HDL-cholesterol, median mg/dl	62 (51–74)	63 (53–75)	48 (41–57)	< 0.001
LDL-cholesterol, median mg/dl	119 (99–140)	117 (98–138)	131 (110–153)	< 0.001
TG, median mg/dl	83 (58–124)	77 (55–109)	173 (125–233)	< 0.001

Note: In the overall cohort, the median age was 54 years (IQR: 47–62), and women accounted for 41.9% of the population. In the MetS subgroup (*N* = 331 793), the median age was higher at 59 years (IQR: 52–66), with women comprising 28.4% of the group. In contrast, in the non-MetS subgroup (*N* = 2 380 777), the median age was 53 years (IQR: 46–61), and women accounted for 43.7%. These distributions highlight age and sex differences associated with the prevalence of MetS in this large-scale population dataset. Values are median (interquartile ranges), and only values of "women" and "smoker" are number (percent). Please note that since the entry time in each subject varied, we could not show the exact year for the entry. Because our database is composed of the annual data from 2005 to 2020. If the entry criteria are matched to the characteristics of the subjects, we enrolled such subjects irrespective of the entry year.
Abbreviations: Abd, abdominal; BMI, body mass index; dBP, diastolic blood pressure; Hb, haemoglobin; HbA1c, haemoglobin A1c; HDL, high density lipoprotein; LDL, low density lipoprotein; sBP, systolic blood pressure; TG, Triglyceride.

29941393, 2026, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lci2.70057, Wiley Online Library on [05/10/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

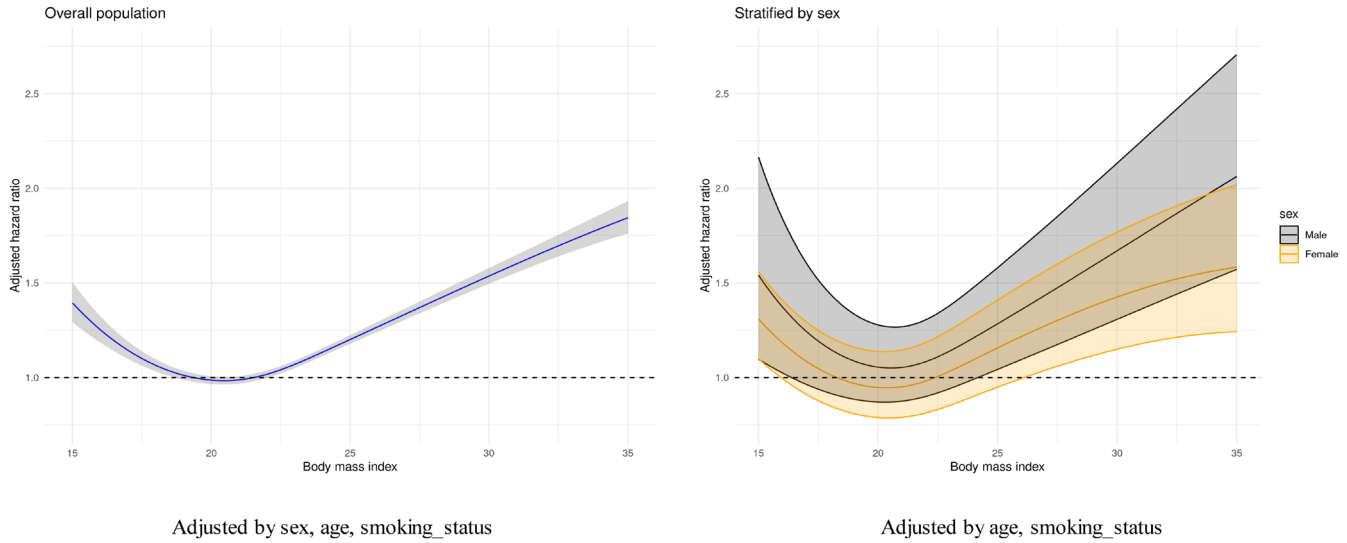


FIGURE 2 | Hazard ratios (HRs) for HCC according to body mass index (BMI). HRs were calculated using a Cox proportional hazards model adjusted for sex, age, and smoking status. The analysis revealed a U-shaped relationship between BMI and liver cancer risk, indicating increased hazards at both low and high BMI levels.

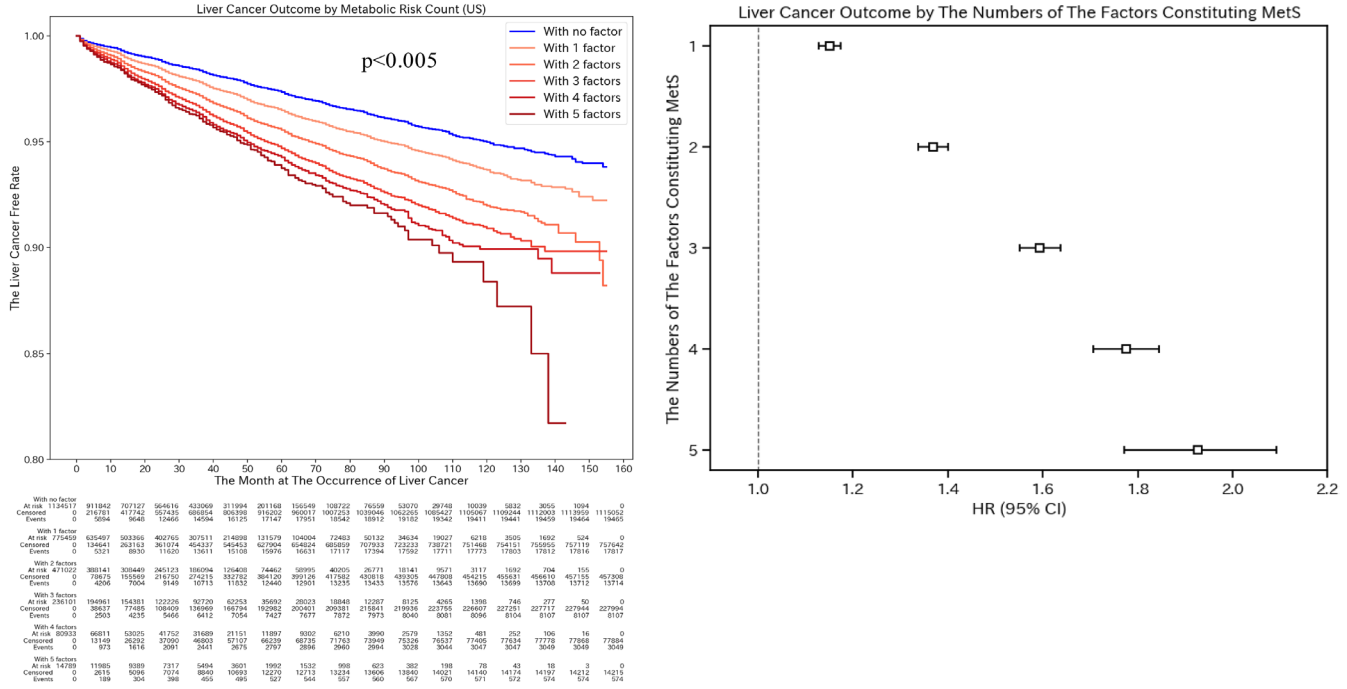


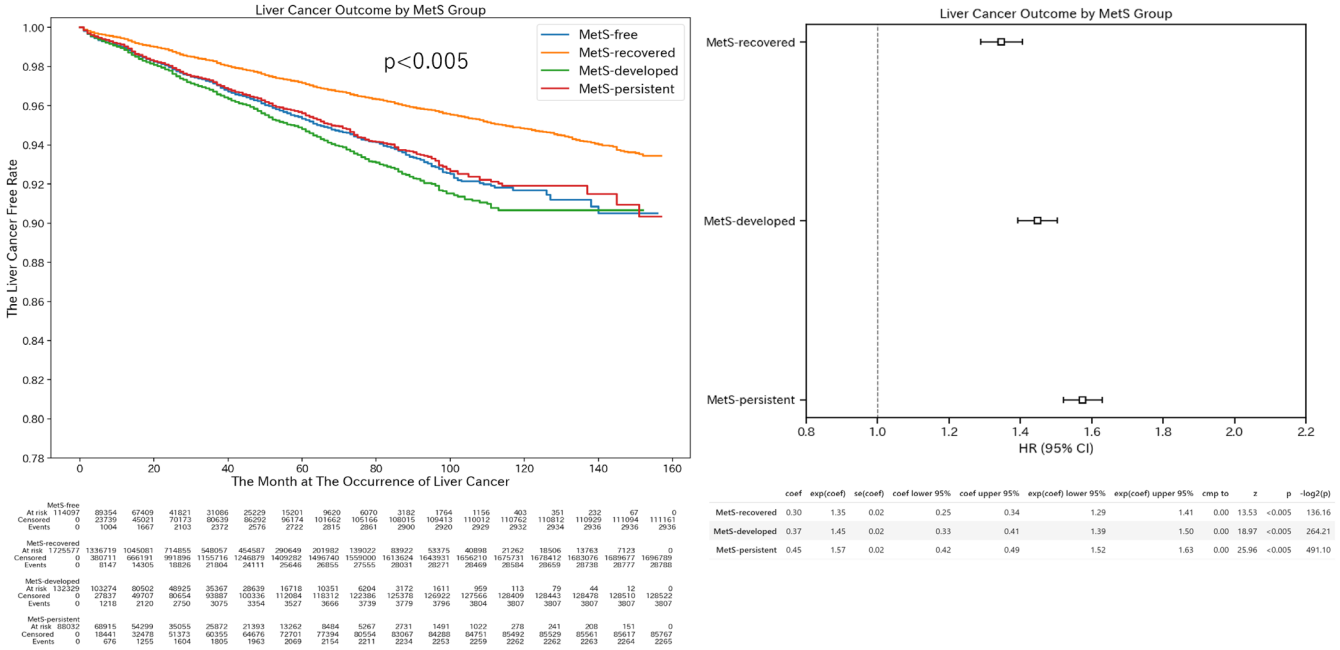
FIGURE 3 | Hazard ratios for liver cancer according to the number of MetS components. An increasing number of MetS components was associated with a stepwise elevation in HRs for liver cancer. This trend was statistically significant ($p < 0.05$).

incidence among the four groups. Using the MetS-free group as the reference, the hazard ratios were 1.35 (95% CI, 1.29–1.41), 1.45 (95% CI, 1.39–1.50), and 1.57 (95% CI, 1.52–1.63) for the MetS-recovered, MetS-developed, and MetS-persistent groups, respectively ($p < 0.05$). The MetS-persistent group showed the highest cumulative incidence of HCC and the greatest risk of HCC (Figure 4). Using the MetS-free group as the reference, the MetS-recovered group remained at increased risk of HCC, although its risk was lower than that of the MetS-developed and MetS-persistent groups. These findings suggest that recovery from MetS may reduce HCC risk relative to persistent or newly developed MetS, but does not appear to restore risk to the level of the MetS-free group.

4 | Discussion

HCC is the sixth most common cancer worldwide and the third leading cause of cancer-related death, making it a significant global public health concern [6]. HCC is a highly complex disease with multiple etiological factors. Major risk factors for HCC include hepatitis B virus (HBV), hepatitis C virus (HCV), autoimmune

29941393, 2026, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lci2.70057, Wiley Online Library on [05/10/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License



	coef	exp(coef)	se(coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%	cmp to	z	p	-log2(p)
MetS-recovered	0.30	1.35	0.02	0.25	0.34	1.29	1.41	0.00	13.53	<0.005	136.16
MetS-developed	0.37	1.45	0.02	0.33	0.41	1.39	1.50	0.00	18.97	<0.005	264.21
MetS-persistent	0.45	1.57	0.02	0.42	0.49	1.52	1.63	0.00	25.96	<0.005	491.10

FIGURE 4 | Hazard ratios for liver cancer across MetS dynamic groups. Participants were classified into four groups based on changes in MetS status over a 4 year period from baseline: MetS-free, MetS-developed, MetS-persistent, and MetS-recovered. HRs for liver cancer differed significantly across these groups ($p < 0.05$), with the highest risk observed in the MetS-persistent group and reduced risk in the MetS-recovered group. * This dynamic analysis included 206 847 of the 2 712 570 participants in the main cohort who underwent health examinations in both 2010–2011 and 2012–2013 and had sufficient data to determine MetS status at both time points. Because this subcohort and its preprocessing differed from those used in the other analyses, the findings should be interpreted within this specific population.

liver diseases, alcoholic liver disease (ALD), T2D, and metabolic dysfunction-associated steatotic liver disease (MASLD) [2].

However, recent advances in direct-acting antiviral (DAA) therapy for HCV have led to a decline in HCV-related HCC incidence [7]. This reduction is attributed to the elimination of the underlying viral cause, which decreases not only hepatic fibrosis but also the risk of carcinogenesis [8]. Therefore, identifying and eliminating factors involved in hepatocarcinogenesis remains critically important for the prevention and management of HCC. In recent years, with the increasing prevalence of MetS, fatty liver disease has emerged as a major etiological factor for chronic liver disease progressing to HCC [4, 9, 10]. Furthermore, T2D is characterized by advanced impairment of glucose metabolism and is regarded as a progressive stage of MetS with clinical continuity. T2D has been reported to double the incidence of HCC and is recognized as an independent risk factor for HCC [11, 12]. With the recent global rise in T2D prevalence, the incidence and burden of HCC are also expected to increase correspondingly [4, 10]. Therefore, because T2D represents an extreme state of metabolic abnormality that exerts a disproportionate impact on HCC risk [11–14], participants with T2D were intentionally excluded from this study. T2D was defined based on a confirmed diagnosis according to the ICD-10 codes or the documented prescription of antidiabetic medications, including insulin, sulfonylureas, and dipeptidyl peptidase-4 (DPP-4) inhibitors. This exclusion enabled us to distinguish the role of T2D from that of MetS in hepatocarcinogenesis and to specifically evaluate the HCC risk attributable to MetS in the absence of T2D.

Given these trends, analysing the association between MetS and HCC, as well as its temporal dynamics is crucial for the prevention and treatment of HCC driven by metabolic dysfunction. To answer these important questions, this study has investigated the incidence of HCC over a 10-year period in a Japanese cohort, comparing individuals with and without MetS to clarify the relationship between MetS and HCC and a role of preMetS for the incidence of HCC. First of all, since obesity plays a central role among the MetS components, we investigated the relationship between BMI and HCC, and found that both lower and higher BMI values were associated with higher incidence compared to the average BMI. Although BMI is not a component of MetS, it is an important obesity-related indicator associated with hepatocarcinogenesis. Because BMI was analysed independently and not used as a substitute for waist circumference, our findings should not be interpreted as evaluating BMI as a surrogate marker of central obesity. In our analysis, the association between BMI and HCC exhibited a U-shaped pattern, with excess risk at both extremes of the BMI spectrum. Consistent with this, Jun et al. reported a nonlinear relationship between adiposity and HCC in a nationwide cohort, demonstrating a clear increase in HCC incidence at BMI $\geq 25\,kg/m^2$ but no linear trend below this threshold [15]. In a large, population-based NAFLD/MASLD cohort, Jung et al. further showed a U-shaped association between BMI (and waist circumference) and incident HCC, with the highest risk observed among underweight individuals and a renewed increase at higher BMI levels [16]. The magnitude of obesity-related HCC risk also varies by sex and ethnicity, as shown in multiethnic analyses [17]. Moreover, higher BMI is independently associated with increased HCC-related mortality and poorer prognosis [18], while Mendelian randomization studies support a causal contribution of adiposity to HCC risk [19]. Taken together, these findings, alongside our

29941393, 2026, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lci2.70057, Wiley Online Library on [05/10/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

data, suggest that both low BMI—likely reflecting frailty or sarcopenia in chronic liver disease—and high BMI—reflecting metabolic and inflammatory injury—are associated with increased risk of HCC.

However, these plausible explanations were not directly evaluated in this study and warrant further investigation in future research. Importantly, our study demonstrated that as the number of MetS components increased from one to five, the incidence of HCC rose in a stepwise manner, and even individuals in the preMetS state exhibited a significant association with HCC. This finding, achieved by excluding the strong confounding effect of T2D, provides robust evidence that the accumulation of MetS components independently contributes to increased HCC risk. Furthermore, the analysis revealed that preMetS itself was also significantly associated with HCC. A PubMed search through June 2026 identified no relevant studies. Therefore, to our knowledge, this is the first large-scale nationwide cohort study to suggest that even the early stages of MetS may contribute to hepatocarcinogenesis.

Although the pathophysiology of MetS, particularly in the context of obesity, especially abdominal obesity, hypertension, dyslipidemia, and DM, is complex, the pathophysiological mechanisms of MetS related to impaired glucose tolerance are closely linked to the development of HCC. Key molecular mechanisms underlying the pathogenesis of MetS include (1) insulin, (2) adiponectin, and (3) reactive oxygen species (ROS) [20]. Insulin is a major anabolic hormone that stimulates cellular proliferation [21]. The pro-tumorigenic effects of insulin in vivo are mediated by indirect mechanisms, notably through the stimulation of insulin-like growth factor 1 (IGF-1). Overexpression of IGF-1 promotes cell proliferation, while its suppression inhibits tumour growth [21]. IGF-1 also activates p21 ras/MAPK signalling pathways that drive cellular proliferation; thus, its proliferative and anti-apoptotic effects contribute to tumorigenesis [22]. Furthermore, obesity promotes insulin resistance through cytokines such as tumour necrosis factor-alpha (TNF-α) secreted by adipocytes. This leads to exacerbation of hyperglycemia, progression of T2D, and hyperinsulinemia, all of which have been implicated in the pathogenesis of HCC [1].

Adipokines, which are secreted by adipocytes, constitute a diverse group of signalling molecules involved in a wide range of biological processes, including appetite regulation, energy homeostasis, inflammation, insulin resistance and sensitivity, angiogenesis, lipid metabolism, cell proliferation, and atherogenesis [23]. Many of these functions are implicated in the pathogenesis of MetS and carcinogenesis [24].

Adiponectin, one of the major adipokines, enhances insulin sensitivity; however, obesity and the expansion of adipose tissue are known to reduce circulating levels of adiponectin [25].

ROS not only play a role in the inflammatory processes of MASH but also cause DNA damage through various mechanisms, including base modifications, deletions, frameshift mutations, strand breaks, DNA-protein crosslinking, and chromosomal rearrangements [26]. Such DNA damage can affect genes involved in cell proliferation, such as *ras*, and genes related to cell survival, such as *p53*, thereby contributing to carcinogenesis and cancer progression. Understanding the temporal dimension through which MetS influences the incidence of HCC is also of critical importance, as the prognosis of MetS is expected to vary significantly depending on the progression or improvement of lifestyle factors. In the present study, by investigating longitudinal dynamics, we demonstrated that persistence, worsening, or improvement of MetS status led to significant differences in HCC incidence. Specifically, the emergence of MetS in individuals previously classified as non- MetS was associated with an increased incidence of HCC, whereas improvement in MetS status was associated with a decreased incidence of HCC. These findings suggest that lifestyle modification and therapeutic intervention for MetS may play a preventive role in HCC development and contribute to improved prognosis. Although the definition of MetS was clarified in this study, no substantive changes were made to its components or thresholds, and the main results were consistent before and after the revision, indicating that the study conclusions are robust. The NCEP/ATPIII definition used in this study does not include LDL-C or lipid-lowering therapy as diagnostic components. However, in clinical practice, a substantial proportion of patients receive statins or other lipid-lowering agents, and incorporating such therapy into the definition of MetS is of considerable importance. Although this study did not directly evaluate this issue, several large-scale observational studies and meta-analyses have demonstrated that statin therapy reduces the incidence of HCC [27, 28]. For example, a meta-analysis reported a 37% reduction in HCC risk among statin users, particularly in high-risk populations with chronic liver disease [27]. Similarly, chemopreventive effects of statins against HCC have been observed in patients with HBV or HCV infection as well as in those with MASLD [28, 29]. Therefore, consideration of patients receiving lipid-lowering therapy is essential for accurate clinical interpretation, and it is possible that such individuals were included in our cohort. Future studies should incorporate lipid-lowering therapy into the operational definition of MetS and assess its impact on HCC risk. Additionally, we cannot exclude the possibility that MetS status changed between the 2012–2013 assessment and the onset of HCC. A further limitation is that changes in MetS during follow-up were evaluated only at limited, fixed time points. Future analyses that incorporate multiple assessments to capture the temporal dynamics of MetS are warranted.

As this was an observational study, a causal relationship between improvement in MetS and reduced HCC risk cannot be definitively established. Therefore, future prospective studies are warranted to clarify this relationship. While the present study clearly supports the importance of cumulative metabolic burden and temporal change in MetS status, the relative contribution of each individual MetS component to hepatocarcinogenesis remains to be elucidated. Further long-term studies are warranted to clarify these component-specific effects and their underlying pathophysiological mechanisms.

Several limitations of this study should be acknowledged. First, because this was a retrospective study, a substantial amount of missing data were present, and participants with incomplete information were excluded from the analysis. HBV and HCV

29941393, 2026, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lci2.70057, Wiley Online Library on [05/10/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

infection, cirrhosis, and alcoholic liver disease are important confounding factors for HCC development. However, because the JMDC database is based on insurance claims data, detailed clinical information, including HBsAg, anti-HBcAb, HCV RNA, fibrosis stage, and quantitative alcohol consumption, was not consistently available, precluding adequate adjustment for these factors. Therefore, patients with documented HBV, HCV, or alcoholic liver disease were excluded before analysis based on ICD-10 codes. Nevertheless, undiagnosed cases could not be completely excluded, and the potential synergistic effects of MetS and chronic viral hepatitis on HCC risk could not be directly assessed. Thus, residual confounding from unmeasured viral hepatitis, alcohol exposure, and related factors may have influenced our findings.

Importantly, the aim of the present study was to evaluate the association between MetS status and incident HCC, rather than to determine the direct aetiology of each HCC case. Because detailed imaging, histology, and full liver-specific phenotyping were unavailable in this database, we could not determine whether each HCC case was directly attributable to hepatic steatosis. This should be considered when interpreting the findings. Secondly, there may be racial or ethnic differences in how MetS influences HCC incidence. However, the high incidence of MASLD-related HCC has been reported not only in Japan but also in East Asia, Southeast Asia, and the United States [10], suggesting that the conclusions of this study may be generalizable across diverse populations.

Third, both the overall study population and the dynamic subcohort may be subject to selection bias. Because the dynamic analysis required repeated health examinations, participants included in this analysis may have differed systematically from those excluded and may represent a more health-conscious and continuously employed population. However, the extracted dataset did not contain sufficient information to formally compare baseline characteristics between participants included in and excluded from the dynamic subcohort. In addition, the overall cohort consisted of employees of general corporations and their family members and may therefore differ from the general Japanese population in age distribution, health awareness, comorbidity profiles, and follow-up patterns. Although the mean age was comparable to the national average in Japan in 2020 (48.9 years), individuals aged $\geq$ 80 years may have been underrepresented. These characteristics may introduce selection bias, limit the generalizability of our findings, and influence competing risks. Therefore, the observed HCC incidence should be interpreted in the context of this study population and should not be directly compared with rates reported in high-risk populations, such as patients with cirrhosis or viral hepatitis.

Fourth, the mean follow-up period of 40.7 months was relatively short and may have limited our ability to assess the long-term risk of HCC. In addition, dynamic MetS status was assessed at only two time points (2010–2011 and 2012–2013), which may not fully capture long-term changes in metabolic status. Furthermore, some participants may have developed T2D during follow-up; however, owing to the database structure, incident diabetes could not be incorporated as a time-dependent covariate. Therefore, the longitudinal effects of changes in MetS and glucose metabolism on HCC risk could not be fully evaluated. Future long-term prospective studies incorporating repeated assessments and time-dependent analyses are warranted.

5 | Conclusion

In conclusion, this study demonstrated a strong association between MetS, its temporal changes, and the incidence of HCC. Furthermore, preMetS was identified as a potential novel risk factor for HCC. These findings may contribute to a better understanding of the association between metabolic dysfunction and hepatocarcinogenesis and underscore the importance of early identification and management of MetS for HCC prevention.

Author Contributions

Y.Y., N.K., and M.K. conceived and designed the study. N.K. conducted the statistical analysis and interpretation. Y.Y. and M.K. drafted the manuscript. All authors reviewed and approved the final version of the manuscript.

Acknowledgements

We extended our sincere appreciation to the dedicated medical staff and processing personnel at the research facilities where the clinical data were gathered. There is no external funding associated with the present study.

Ethics Statement

The entire research protocol was approved by the Institutional Ethics Committee of Hanwa Memorial Hospital. This study was conducted in accordance with the Clinical Research Guidelines outlined by the Ministry of Health, Labour and Welfare of Japan through a retrospective analysis of database records. All procedures were carried out in accordance with the Declaration of Helsinki.

Consent

Prior to obtaining approval from the Clinical Research Committee, informed consent was obtained from each participant using an opt-out method. After ethical approval was granted, written informed consent was secured. To protect patient confidentiality, all data were anonymized before analysis.

Conflicts of Interest

Masafumi Kitakaze has received personal fees from AstraZeneca, Takeda, and Eli Lilly. The remaining authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study were obtained from the JMDC database. Because the JMDC database is proprietary and subject to licensing restrictions, the raw data cannot be made publicly available. Qualified researchers may apply for access directly through JMDC under an appropriate data use agreement.

References

1. A. Marengo, C. Rosso, and E. Bugianesi, "Liver Cancer: Connections With Obesity, Fatty Liver, and Cirrhosis," *Annual Review of Medicine* 67 (2016): 103–117.

29941393, 2026, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lci2.70057, Wiley Online Library on [05/10/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2. S. Yamasaki, T. Nakahara, M. Tsuge, et al., "Metabolic Dysfunction-Associated Steatotic Liver Disease Affects the Development of Hepatocellular Carcinoma After Sustained Virologic Response in Chronic Hepatitis C Patients," *Journal of Gastroenterology* 60, no. 8 (2025): 1014–1025.

3. Y. Miyashita, T. Hitsumoto, H. Fukuda, et al., "Metabolic Syndrome Is Linked to the Incidence of Pancreatic Cancer," *EClinicalMedicine* 67 (2023): 102353.

4. K. A. McGlynn, J. L. Petrick, and H. B. El-Serag, "Epidemiology of Hepatocellular Carcinoma," *Hepatology* 73, no. 1 (2021): 4–13.

5. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, "Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)," *Journal of the American Medical Association* 285, no. 19 (2001): 2486–2497.

6. F. Bray, M. Ravelsanne, H. Song, et al., "Global Cancer Statistics 2022: GLOBOCAN Estimates Incidence and Mortality Worldwide for 185 Cancers in 36 Countries," *CA: A Cancer Journal for Clinicians* 74, no. 3 (2024): 229–263.

7. A. Forner, M. Reig, and J. Bruix, "Hepatocellular Carcinoma," *Lancet* 391, no. 10127 (2018): 1301–1314.

8. M. P. Manns and B. Maasoumy, "Breakthroughs in Hepatitis C Research: From Discovery to Cure," *Nature Reviews. Gastroenterology & Hepatology* 19, no. 8 (2022): 533–550.

9. D. Q. Huang, H. B. El-Serag, and R. Loomba, "Global Epidemiology of NAFLD-Related HCC: Trends, Predictions, Risk Factors and Prevention," *Nature Reviews. Gastroenterology & Hepatology* 18, no. 4 (2021): 223–238.

10. E. Y. Tan, P. Danpanichkul, and J. N. Yong, "Liver Cancer in 2021: Global Burden of Disease Study," *Journal of Hepatology* 82, no. 5 (2025): 851–860.

11. P. Wang, D. Kang, W. Cao, Y. Wang, and Z. Liu, "Diabetes Mellitus and Risk of Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis," *Diabetes/Metabolism Research and Reviews* 28 (2012): 109–122.

12. C. Wang, X. Wang, G. Gong, et al., "Increased Risk of Hepatocellular Carcinoma in Patients With Diabetes Mellitus: A Systematic Review and Meta-Analysis of Cohort Studies," *International Journal of Cancer* 130, no. 7 (2012): 1639–1648.

13. H. B. El-Serag, H. Hampel, F. Javadi, et al., "The Association Between Diabetes and Hepatocellular Carcinoma: A Systematic Review of Epidemiologic Evidence," *Clinical Gastroenterology and Hepatology* 4, no. 3 (2006): 369–380.

14. T. G. Simon, L. Y. King, D. Q. Chong, et al., "Diabetes, Metabolic Comorbidities, and Risk of Hepatocellular Carcinoma: Results From Two Prospective Cohort Studies," *Hepatology* 67 (2018): 1797–1806.

15. B. G. Jun, M. Kim, H. S. Shin, J. J. Yi, and S. W. Yi, "Impact of Overweight and Obesity on the Risk of Hepatocellular Carcinoma: A Prospective Cohort Study in 14.3 Million Koreans," *British Journal of Cancer* 127 (2022): 109–115.

16. H. N. Jung, J. H. Heo, E. Roh, et al., "Risk of Hepatocellular Carcinoma According to Body Mass Index and Waist Circumference in Nonalcoholic Fatty Liver Disease," *World journal of gastrointestinal oncology* 17, no. 6 (2025): 107364.

17. V. W. Setiawan, U. Lim, L. Lipworth, et al., "Sex and Ethnic Differences in the Association of Obesity With Risk of Hepatocellular Carcinoma," *Clinical Gastroenterology and Hepatology* 14, no. 2 (2016): 309–316.

18. A. Gupta, A. Das, K. Majumder, et al., "Obesity Is Independently Associated With Increased Risk of Hepatocellular Cancer-Related Mortality: A Systematic Review and Meta-Analysis," *American Journal of Clinical Oncology* 41, no. 9 (2018): 874–881.

19. L. Wei, E. Ding, D. Lu, Z. Rui, J. Shen, and G. Fan, "Assessing the Effect of Modifiable Risk Factors on Hepatocellular Carcinoma: Evidence From a Bidirectional Mendelian Randomization Analysis," *Discover Oncology* 16 (2025): 437.

20. S. Cowey and R. W. Hardy, "The Metabolic Syndrome: A High-Risk State for Cancer?," *American Journal of Pathology* 169, no. 5 (2006): 1505–1522.

21. P. E. Clayton, I. Banerjee, P. G. Murray, and A. G. Renehan, "Growth Hormone, the Insulin-Like Growth Factor Axis, Insulin and Cancer Risk," *Nature Reviews. Endocrinology* 7, no. 1 (2011): 11–24.

22. Y. H. Ibrahim and D. Yee, "Insulin-Like Growth Factor-I and Cancer Risk," *Growth Hormone & IGF Research* 14, no. 4 (2004): 261–269.

23. P. Trayhurn and I. S. Wood, "Adipokines: Inflammation and the Pleiotropic Role of White Adipose Tissue," *British Journal of Nutrition* 92, no. 3 (2004): 347–355.

24. A. R. de Oliveira Dos Santos, B. de Oliveira Zanuso, V. F. Bordin Miola, et al., "Adipokines, Myokines, and Hepatokines: Crosstalk and Metabolic Repercussions," *International Journal of Molecular Sciences* 22, no. 5 (2021): 2639.

25. M. Iwabu, M. Okada-Iwabu, T. Yamauchi, and T. Kadowaki, "Adiponectin/Adiponectin Receptor in Disease and Aging," *npj Aging and Mechanisms of Disease* 1 (2015): 15013.

26. M. Valko, M. Izakovic, M. Mazur, C. J. Rhodes, and J. Telser, "Role of Oxygen Radicals in DNA Damage and Cancer Incidence," *Molecular and Cellular Biochemistry* 266, no. 1–2 (2004): 37–56.

27. S. Singh, P. P. Singh, A. G. Singh, M. H. Murad, and W. Sanchez, "Statins Are Associated With a Reduced Risk of Hepatocellular Cancer: A Systematic Review and Meta-Analysis," *Gastroenterology* 144, no. 2 (2013): 323–332.

28. G. Kim, S. Y. Jang, C. M. Nam, and E. S. Kang, "Statin Use and the Risk of Hepatocellular Carcinoma in Patients at High Risk: A Nationwide Nested Case-Control Study," *Journal of Hepatology* 68, no. 3 (2018): 476–484.

29. Y. T. Tsan, C. H. Lee, J. D. Wang, and P. C. Chen, "Statins and the Risk of Hepatocellular Carcinoma in Patients With Hepatitis B Virus Infection," *Journal of Clinical Oncology* 30, no. 6 (2012): 623–630.

29941393, 2026, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lci2.70057, Wiley Online Library on [05/10/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License