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ORIGINAL RESEARCH

Metabolic syndrome and the incidence of hepatocellular carcinoma: a meta-analysis of cohort studies

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Background: Patients with metabolic syndrome (MetS) were suggested to have a higher risk of hepatocellular carcinoma (HCC), although the results of previous cohort studies are not consistent.

Aim: To perform an updated meta-analysis to evaluate the association between MetS and subsequent incidence of HCC.

Methods: Relevant cohort studies were identified by searching PubMed and Embase databases. Cochrane's Q-test and I^2 statistic were used to analyze the heterogeneity. Random effects model was used for the meta-analysis.

Results: Six cohort studies with 127,198 participants and 1,293 HCC cases during follow-up were included. Patients with MetS had a significantly higher incidence of HCC in studies with MetS defined by the revised National Cholesterol Education Program's Adults Treatment Panel III (risk ratio [RR]: 1.43, 95% CI: 1.19–1.72, $p<0.001$; $I^2=29\%$) or International Diabetes Federation criteria (RR: 1.59, 95% CI: 1.13–2.23, $p=0.008$; $I^2=0\%$). Results of subgroup analysis showed that the presence of MetS was associated with a higher incidence of HCC in males (RR: 1.75, 95% CI: 1.28–2.38, $p<0.001$) but not in females (RR: 1.18, 95% CI: 0.76–1.84, $p=0.46$), and the association between MetS and higher risk of HCC was consistent regardless whether alcohol intake was adjusted. Although both were significant, MetS conferred higher risk of HCC in carriers of hepatitis B virus when compared with general population ($p=0.06$).

Conclusion: The presence of MetS is associated with significantly increased incidence of HCC in male participants.

Keywords: metabolic syndrome, hepatocellular carcinoma, cohort study, meta-analysis

Introduction

Although different diagnostic criteria are applied, metabolic syndrome (MetS) is defined as the presence of a cluster of disorders of metabolism, including obesity, hypertension, hyperglycemia, and dyslipidemia.[1–3] Pathophysiologically, one of the key mechanisms underlying the development of MetS is insulin resistance, and a chronically activated inflammatory status has been involved in the pathogenesis of many other clinical disorders in patients with MetS.[4,5] Since the prevalence of MetS is reported to be relatively high (between 10% and 30% in adult population) in both the developed and developing countries,[6–8] intensive understanding of the risks of chronic diseases in these patients is important for improving the general health status in the global population. Accumulating evidence from epidemiological studies indicates that the patients with MetS are at higher risk for the development of chronic diseases, including cardiovascular diseases,[9] stroke,[10] osteoporosis,[11] and venous thromboembolism.[12]

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Moreover, since low-grade inflammatory response has to be involved in the pathogenesis of cancer,[13] patients with MetS have been suggested to be with higher risk for the development of cancer. Indeed, patients with Mets are indicated to be of higher risks of colorectal, pancreatic, breast, endometrial, and prostate cancers as evidenced by the results of previous observational studies.[14–19] However, the association between MetS and the subsequent risk of hepatocellular carcinoma (HCC) is not completely determined according to findings of previous studies.[15,20] Although results of early meta-analyses of observational studies suggested that the presence of MetS may be associated with higher risk of HCC,[15,20] they included both the cohort[20–23] and the case–control[24] studies, and therefore, a sequential relationship between the presence of MetS at baseline and subsequent incidence of HCC could not be indicated. Moreover, one[15] of the previous meta-analyses included a cohort study with the outcome of HCC-related mortality[25] instead of HCC incidence. Since many potential factors may influence the outcome of HCC-related mortality, such as the application of anticancer treatments, the potential association between MetS and HCC risk may be confounded. In addition, the available studies included in the previous meta-analyses are limited, which prevented the investigations regarding the potential study characteristics on the association between MetS and HCC risk. Since some recently published related cohort studies have not been included in the previous meta-analyses,[26,27] we aimed to perform an updated meta-analysis to evaluate the association between MetS and subsequent incidence of HCC. Moreover, whether the association between MetS and HCC is confounded by established risk factors for HCC, including alcohol intake[28] and hepatitis viruses,[29] is also explored in this study.

Methods

The meta-analysis was performed in accordance with the Meta-analysis of Observational Studies in Epidemiology[30] and *Cochrane's Handbook*[31] guidelines.

Literature searching

Databases of PubMed and Embase were searched for relevant records, using the terms "metabolic syndrome", "insulin resistance syndrome", or "syndrome X", combined with "cancer", "neoplasm", "carcinoma", and "hepatocellular", "hepatic", "intrahepatic", "interlobular", or "liver", as well as "prospective", "prospectively", "retrospective", "retrospectively", "followed", "follow-up", "cohort", or "cohorts". The searching was limited to studies in humans and those published in English language. The reference lists of original and review articles were also analyzed using a manual approach. The final literature search was performed on October 22, 2017.

Study selection

Articles were included in the meta-analysis if they met all of the following criteria: 1) published as full-length article in English; 2) reported as cohort studies (prospective or retrospective, regardless of sample size) with the follow-up duration of at least 1 year; 3) included adult population (≥18 years of age) without HCC at baseline; 4) MetS defined according to the criteria of the original articles was identified as exposure of interest at baseline; 5) participants without MetS at baseline were used as controls; 6) documented the incidences of HCC during follow-up; and 7) reported the adjusted risk ratios (RRs, at least adjusted for age) and their corresponding 95% CIs for the incidence of HCC comparing individuals with MetS at baseline to those without MetS. Reviews, letters, editorials, and studies with designs other than cohort study were excluded.

Data extraction and quality evaluation

Literature searching, data extraction, and quality assessment of the included studies were performed according to the predefined inclusion criteria. Discrepancies were resolved by consensus. Data that were extracted include 1) name of first author, year of publication, and country where the study was performed; 2) design characteristics (prospective or retrospective); 3) characteristics and numbers of the participants; 4) criteria for the diagnosis of MetS; 5) follow-up period; 6) number of HCC cases in each study; and 7) variables adjusted when presenting the results. The quality of each study was evaluated using the Newcastle–Ottawa Scale (NOS),[32] which ranges from 1 to 9 stars and judges each study regarding three aspects: selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest.

Statistical analyses

We used RRs as the general measure for the association between MetS at baseline and the incidence of HCC. Data of RRs and their corresponding standard errors (SEs) were calculated from 95% CIs or *p*-values and were logarithmically transformed to stabilize variance and normalize the distribution.[31] The Cochrane's Q-test and I^2-test were used to evaluate the heterogeneity among the included cohort studies.[31,33] A significant heterogeneity was considered if $I^2>50\%$. We used a random effects model to synthesize the RR data because this model is considered as a

more generalized method that incorporates the potential heterogeneity.[31] Sensitivity analyses, by removing individual study one at a time, were performed to test the robustness of the results.[34] Predefined subgroup analyses were performed to evaluate whether the association between MetS and HCC incidence was affected by gender of the participants, locations of the studies, study design characteristics, population characteristics, and adjustment for alcohol intake, in view of the fact that alcohol intake has been proven to be an important risk factor for HCC.[28] Moreover, potential publication bias was assessed by funnel plots with the Egger regression asymmetry test.[35] We used the RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and STATA software for the meta-analysis and statistics.

Results

Literature searching

The flowchart of database searching is presented in Figure 1. Briefly, 1,392 articles were found via initial literature searching of the PubMed and Embase databases, and 1,362 were excluded through screening of the titles and abstracts mainly because they were not relevant to the purpose of the meta-analysis. Subsequently, 30 potential relevant records underwent full-text review. Of these, 24 were further excluded because two of them were case–control studies, three were not with exposure of MetS, 16 reported the risks of total or other types of cancer, and the other three reported the incidence of HCC-related mortality. Finally, six cohort studies were included.[20–23,26,27]

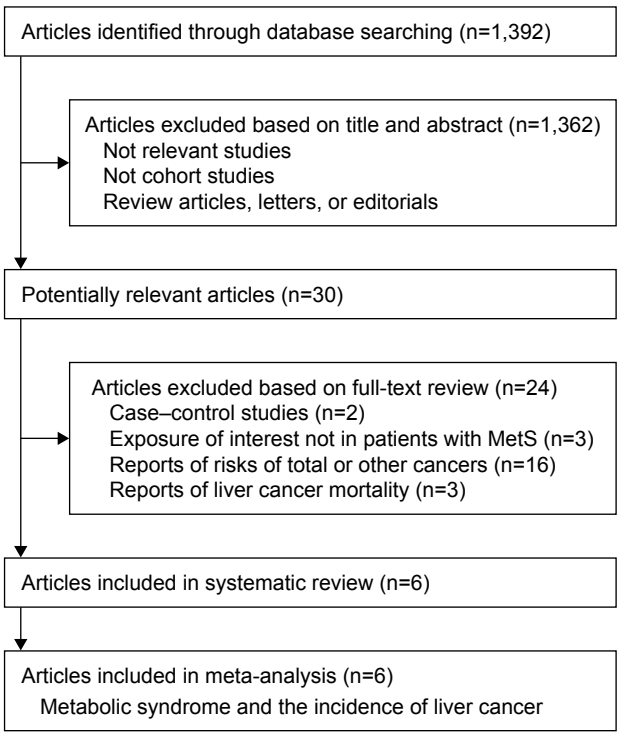

Figure 1 Flowchart of database searching and study identification.
Abbreviation: MetS, metabolic syndrome.

Study characteristics and quality evaluation

The characteristics of the included studies are summarized in Table 1. Overall, we included six cohort studies[20–23,26,27] with 127,198 participants. During follow-up, 1,293 HCC cases were reported. Briefly, four[21,23,26,27] of the included cohort studies were performed in Asian countries, while the other two were performed in Western countries.[20,22] As for the study design, four[20–22,27] were prospective cohorts, while the other two[23,26] were retrospective cohort studies. Five studies[20–23,26] included general population, while the other one[27] included male participants carrying hepatitis B virus (HBV). All of the included studies were adjusted for age and gender when reporting the association between MetS and HCC incidence, while other potential confounding factors such as smoking status, alcohol intake, and physical activities were adjusted in a few other studies. MetS was defined based on the criteria of revised National Cholesterol Education Program's Adults Treatment Panel III (NCEP-ATP III) in all of the included cohorts,[2] while two studies also applied the diagnostic criteria of International Diabetes Federation (IDF) for MetS.[1] Gender-specific associations between MetS at baseline and incidence of HCC during follow-up were reported in all of the included cohorts. The qualities of the included studies were generally good, with the NOS varying between 7 and 9 points.

Association between the revised NCEP-ATP III-defined MetS and HCC risk

The pooled results of six cohorts consisted of nine data sets indicating that MetS defined by the revised NCEP-ATP III criteria was associated with significantly increased risk of HCC incidence (adjusted RR: 1.43, 95% CI: 1.19–1.72, $p<0.001$; Figure 2A) with moderate heterogeneity (p for Cochrane's Q-test=0.19, I^2=29%). Results of subgroup analysis according to the gender of the participants showed that MetS at baseline was associated with higher incidence of HCC during follow-up in men (adjusted RR: 1.75, 95% CI: 1.28–2.38, $p<0.001$, I^2=65%; Figure 2B) but not in women (adjusted RR: 1.18, 95% CI: 0.76–1.84, p=0.46, I^2=57%; Figure 2B). However, the differences between the two subgroups were not significant (p for subgroup difference=0.16). Results of subsequent subgroup analysis indicated that MetS

Table 1 Characteristics of included cohort studies

Study	Country	Design	Characteristics of participants	Number of participants	Definition of MetS	Follow-up period, years	Diagnosis of HCC	HCC cases	Outcome reported	Variables adjusted	NOS
Russo et al,[20] 2008	Italy	PC	Community-based population >40 years	16,677	NCEP-ATP III	1999–2005	Local cancer registry	38	M, F, T	Age and gender	7
Inoue et al,[21] 2009	Japan	PC	Community-based population	27,724	NCEP-ATP III and IDF	1990–2004	National cancer registries	114	M, F	Age, gender, study area, smoking status, alcohol intake, daily total physical activity level, and TC	9
Osaki et al,[23] 2012	Japan	RC	General health examinees	38,832	NCEP-ATP III and IDF	1992–2007	Tottori prefectural cancer registry	129	M, F	Age, gender, smoking status, and alcohol intake	9
Borena et al,[22] 2012	Norway, Austria, and Sweden	PC	Community-based population	578,700	NCEP-ATP III	1972–2005	National cancer registries	266	M, F, T	Age, gender, study cohort, and smoking	8
Ko et al,[26] 2016	Korea	RC	National sample cohort for health check-up	99,565	NCEP-ATP III	2002–2013	Local cancer registry	588	M, F	Age, gender, smoking status, alcohol intake, and exercise	9
Yu et al,[27] 2017	China	PC	Male civil servants carrying HBV	1,690	NCEP-ATP III	1989–2010	National cancer registries	158	M	Age, smoking status, alcohol intake, and family history of HCC	9

Abbreviations: F, female; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IDF, International Diabetes Federation; M, male; MetS, metabolic syndrome; NCEP-ATP III, National Cholesterol Education Program's Adults Treatment Panel III; NOS, the Newcastle–Ottawa Scale; PC, prospective cohort; RC, retrospective cohort; T, total; TC, total cholesterol.

at baseline was significantly associated with higher incidence of HCC in studies of Asian countries (adjusted RR: 1.58, 95% CI: 1.18–2.12, p=0.002), or in studies of prospective design (adjusted RR: 1.41, 95% CI: 1.15–1.72, $p<0.001$), but not in studies of Western countries, or in studies of retrospective design (Table 2). Moreover, we found that the association between MetS at baseline and increased risk of HCC was stronger in studies of HBV carriers (adjusted RR: 2.61, 95% CI: 1.34–5.08, p=0.005) when compared with those of general population (adjusted RR: 1.36, 95% CI: 1.16–1.58, $p<0.001$; p for subgroup difference=0.06; Table 2). However, the association between MetS at baseline and the increased risk of HCC was not significantly affected by whether alcohol intake was adjusted (p for subgroup difference=0.26; Table 2).

Association between IDF-defined MetS and HCC risk

Two studies[21,23] reported the association between IDF-defined MetS and HCC risk. The results of pooled analysis indicated that IDF-defined MetS was associated with significantly increased risk of HCC incidence (adjusted RR: 1.59, 95% CI: 1.13–2.23, p=0.008, I^2=0%; Figure 3). The association between IDF-defined MetS and the risk of HCC incidence was not significantly affected by the gender of participants (p for subgroup difference=0.96; Figure 3).

Publication bias

The funnel plots regarding MetS diagnosed by revised NCEP-ATP III or IDF criteria at baseline and risk of HCC incidence are shown in Figure 4A and B. The funnel plots are symmetric on visual inspection, suggesting low chance of significant publication bias. Results of Egger's regression test suggested that no significant publication bias was detected for the meta-analysis of the association between MetS diagnosed by revised NCEP-ATP III and HCC risk (p=0.64). Egger's regression test was not performed for the meta-analysis of association between IDF-defined MetS and the subsequent risk of HCC since limited cohorts were included.

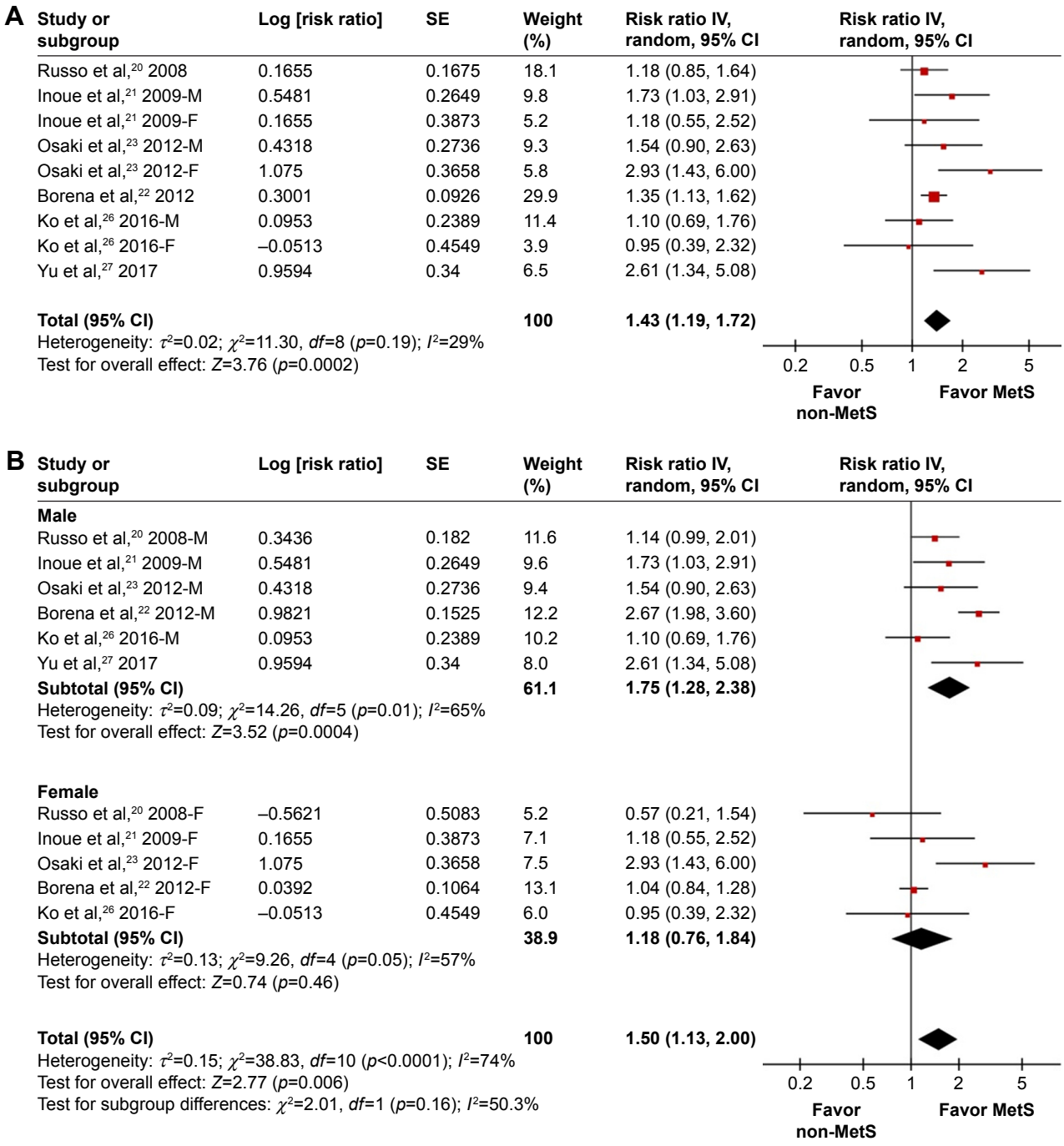

Figure 2 Forest plots for the meta-analysis of the association between the revised NCEP-ATP III-defined MetS and HCC risk.
Notes: (**A**) Forest plots for the overall participants; (**B**) forest plots for the subgroup analysis by gender.
Abbreviations: HCC, hepatocellular carcinoma; MetS, metabolic syndrome; NCEP-ATP III, National Cholesterol Education Program's Adults Treatment Panel III; SE, standard error.

Discussion

In this updated meta-analysis, by pooling the results of all available cohort studies, results of our meta-analysis showed that baseline presence of MetS defined by either the revised NCEP-ATP III or the IDF criteria is associated with significantly higher risk of HCC incidence when compared with general population without MetS at baseline. Moreover, results of subsequent subgroup analysis by gender showed that MetS increased the risk of HCC incidence in male participants, but not in the females. Results of other subgroup analyses indicated that the association between MetS and higher risk of HCC was consistent in studies from Asian countries, of prospective design, and those with or without adjustment for alcohol intake when presenting the results.

Table 2 Subgroup analysis for the association between NCEP-ATP III-defined MetS and the incidence of HCC

Variables	Dataset number	RR (95% CI)	*p* for subgroup effect	I^2	*p* for subgroup difference
Study location					
Asian countries	7	1.58 (1.18, 2.12)	0.002	35%	
Western countries	4	1.34 (0.78, 2.33)	0.29	90%	0.60
Design					
Prospective	5	1.41 (1.15, 1.72)	<0.001	25%	
Retrospective	4	1.47 (0.94, 2.27)	0.09	49%	0.87
Study population					
General population	8	1.36 (1.16, 1.58)	<0.001	9%	
HBV carriers	1	2.61 (1.34, 5.08)	0.005	–	0.06
Adjustment for alcohol intake					
Yes	7	1.58 (1.18, 2.12)	0.002	35%	
No	2	1.31 (1.12, 1.53)	<0.001	0%	0.26

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MetS, metabolic syndrome; NCEP-ATP III, National Cholesterol Education Program's Adults Treatment Panel III; RR, risk ratio.

Importantly, although both are significant, we found that MetS confers higher risk of HCC incidence in HBV carriers when compared with the general population. These results suggested that participants with MetS are at higher risk for the development of HCC, particularly in male participants and in those of HBV carriers.

Our meta-analysis has the following strengths when compared with the previous ones.[15,36] First, we included cohort studies only. Therefore, a sequential association between baseline presence of MetS and the incidence of HCC could be confirmed. Second, cohort studies with HCC-related mortality as the primary outcome were excluded. Therefore, the potential confounding effects of mortality-related factors such as the anticancer treatment could be avoided. Third, we evaluated the associations between MetS defined by two different criteria and the risk of HCC incidence, and the consistent results indicated the robustness of our findings. Lastly, two recently published cohort studies were included, which enables us to perform the subgroup analysis to explore the influences of study or patient characteristics on the association between MetS and HCC incidence.

Overall, the results of our study indicated that the presence of MetS is associated with significantly increased risk of HCC incidence compared with those without MetS.

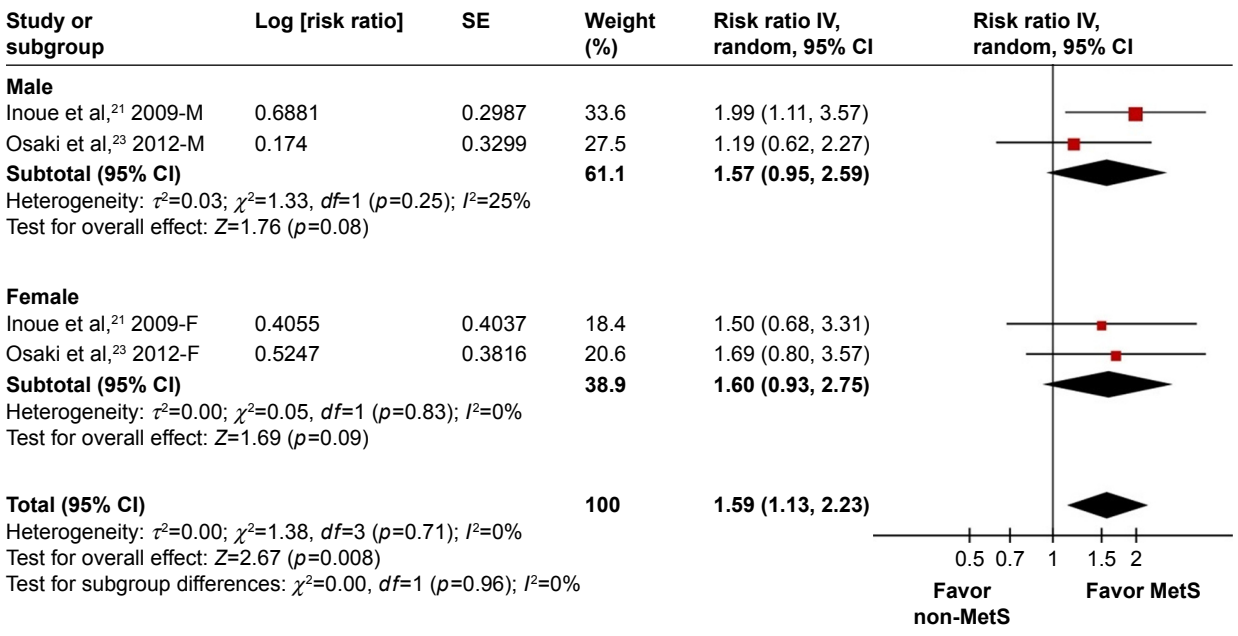

Figure 3 Forest plots for the meta-analysis of the association between IDF-defined MetS and HCC risk stratified by gender.
Abbreviations: HCC, hepatocellular carcinoma; IDF, International Diabetes Federation; MetS, metabolic syndrome.

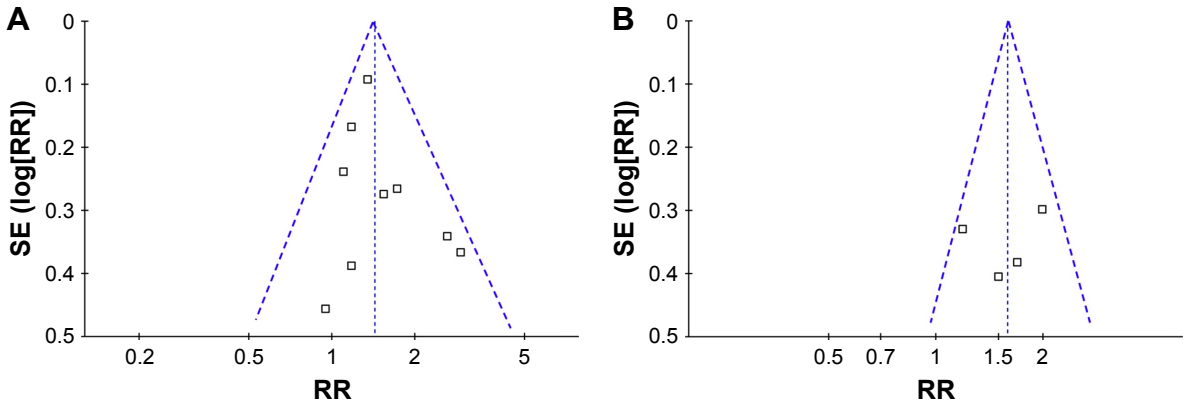

Figure 4 Funnel plots for the meta-analysis of the association between the MetS and HCC risk.
Notes: (**A**) NCEP-ATP ill-defined MetS; (**B**) IDF-defined MetS.
Abbreviations: HCC, hepatocellular carcinoma; IDF, International Diabetes Federation; MetS, metabolic syndrome; NCEP-ATP III, National Cholesterol Education Program's Adults Treatment Panel III; RR, risk ratio; SE, standard error.

These results suggest that intensified prevention of HCC in patients may be needed. The potential association between MetS and HCC risk may be explained by the findings that some components of MetS may have a close relationship with HCC risk. Indeed, a recently published meta-analysis showed that premorbid obesity may be independently associated with a twofold risk of HCC-related mortality.[37] Moreover, patients with type 2 diabetes mellitus (T2DM) are also found to be at higher risk for development of HCC,[38] and some medications against T2DM, such as metformin,[39] may be preventative against HCC. Although the association between dyslipidemia and HCC risk was not fully understood, the classic cholesterol-lowering medication statins were found to be preventative of HCC development.[40] As for the potential mechanisms underlying the association between MetS and the increased risk of HCC development, further researches are needed because the exact mechanisms remain to be determined. The low-grade inflammatory response may be responsible for the carcinogenesis in patients with MetS.[13] Moreover, with the presence of MetS in the liver, occurrence of nonalcoholic fatty liver disease may also expose the patients to increased risk of HCC.[41,42] Besides, as a key pathophysiological mechanism of MetS, insulin resistance has also been suggested to be an important risk factor of HCC pathogenesis.[43,44] Further studies are needed to clarify the dominant mechanisms.

Results of subgroup analysis suggested that MetS may increase the risk of HCC in men but not in women. This is consistent with the findings of some previous studies which indicated that components of MetS may confer higher risk of HCC in male participants than in females. For example, results of a previous meta-analysis showed that the association between obesity and HCC risk was more pronounced in men than in women.[45] However, the underlying mechanisms remain unclear. Furthermore, we found that the association between MetS and increased risk of HCC remains significant in studies with alcohol intake adjusted and more pronounced in carriers of HBV. These results suggest that MetS also increased the risk of HCC in high-risk patients including HBV carriers. Again, these results highlight the importance of intensified HCC prevention in MetS, particularly in high-risk patients, such as the HBV carriers.

Besides above strengths and implications, our meta-analysis has limitations that should be considered when interpreting the results. First, the number of the included cohort studies was relatively small. Therefore, results of subgroup analyses should be interpreted with caution, and large-scale cohort studies are needed to confirm these findings. Second, although most-adequately adjusted results were pooled, we could not exclude other factors, such as the treatment against the components of MetS, which may confound the association between MetS and increased risk of HCC. Third, as inherited in meta-analysis of observational studies, results of our study could only support a sequential association between MetS at baseline and increased risk of HCC incidence subsequently. A causative relationship between MetS and HCC pathogenesis could not be indicated by our findings. Fourth, although MetS defined by revised NCEP-ATP III or IDF criteria was associated with higher HCC incidence, association between MetS defined by other criteria and subsequent HCC incidence remains undetermined. Fifth, studies in our meta-analysis mostly included general population, of which the prevalence of cirrhosis was not reported. Moreover, the

prevalence of cirrhosis at baseline for participants with and without MetS was not adjusted when reporting the association between MetS and risk of HCC. Since cirrhosis is one of the primary risk factors for the development of HCC, we were unable to determine if the prevalence of cirrhosis may confound the association between MetS and HCC. Finally, the prevalence of hepatitis B and C of the participants was not reported in most of our included studies, and these factors were not adjusted when reporting the results. The potential higher prevalence of hepatitis B and C in Asian participants when compared with the participants from Western countries may at least partially be the reason that MetS and increased risk of HCC were significant in studies from Asian countries but not in Western countries. These hypotheses should be evaluated in future studies.

Conclusion

Results of our meta-analysis showed that the presence of MetS is significantly associated with increased risk of HCC incidence when compared with those without MetS at baseline. Intensified HCC prevention in MetS patients, particularly in high-risk patients such as the HBV carriers, may be clinically important.

Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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