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Metabolic syndrome and hepatocellular carcinoma risk

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Background: Hepatocellular carcinoma (HCC) has been associated to diabetes and obesity, but a possible association with the metabolic syndrome (MetS) and its potential interaction with hepatitis is open to discussion.

Methods: We analysed data from an Italian case–control study, including 185 HCC cases and 404 controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed from unconditional logistic regression models.

Results: Among the MetS components, diabetes and obesity (i.e, body mass index (BMI) $\geqslant 30\,kg\,m^{-2}$) were positively associated to HCC risk, with ORs of 4.33 (95% CI, 1.89–9.86) and 1.97 (95% CI, 1.03–3.79), respectively. The ORs for the MetS were 4.06 (95% CI, 1.33–12.38) defining obesity as BMI $\geqslant 25$, and 1.92 (95% CI, 0.38–9.76) defining it as BMI $\geqslant 30$. The risk increased with the number of MetS components, up to an almost four-fold excess risk among subjects with $\geqslant 2$ MetS factors. Among subjects without chronic infection with hepatitis B and/or C, the OR for those with $\geqslant 2$ MetS components was over six-fold elevated. There was no consistent association in subjects with serological evidence of hepatitis B and/or C infection.

Conclusion: This study found that the risk of HCC increases with the number of MetS components in subjects not chronically infected with hepatitis viruses.

Worldwide, liver cancer is the third most common cause of cancer death among men and the sixth one among women (Llovet *et al*, 2003; London and McGlynn, 2006). Hepatocellular carcinoma (HCC) is the most frequent histologic type of primary liver cancer (Stuver and Trichopoulos, 2008), accounting for up to 85% of cases. The predominant role of chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) in the aetiology of HCC is well documented (Llovet *et al*, 2003; London and McGlynn, 2006; Mueller *et al*, 2006). Advanced age, male gender, heavy alcohol drinking, tobacco smoking and cirrhosis are other important recognised HCC risk factors (Llovet *et al*, 2003; London & McGlynn, 2006; Mueller *et al*, 2006).

The metabolic syndrome (MetS) is a series of metabolically related conditions, consistently associated with an increased risk of cardiovascular diseases (Alberti *et al*, 2006, 2009). Since the late 90s, several definitions have been developed for MetS; these were based on glucose intolerance–hyperglycemia–diabetes, obesity, hypertension and dyslipidemia, but differed in the details and

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criteria (Alberti and Zimmet, 1998; Third Report of the NCEP Expert Panel, 2002; Alberti *et al*, 2005; Grundy *et al*, 2005). MetS components reflect overnutrition and sedentary lifestyle resulting in excess adiposity. A consensus statement by the major scientific associations in the field of metabolic disorders proposed common criteria for the clinical diagnosis of the MetS ('joint interim statement'), that is, the presence of at least three of the following conditions: elevated waist circumference (for abdominal obesity), elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, elevated blood pressure, and elevated fasting glucose (Alberti *et al*, 2009). Several epidemiological studies reported positive associations between obesity and diabetes and the risk of primary liver cancer, whereas data on the association with other MetS components are scanty (Adami *et al*, 1996; Wideroff *et al*, 1997; Lagiou *et al*, 2000; El-Serag *et al*, 2004; Yuan *et al*, 2004; Lai *et al*, 2006; Larsson and Wolk, 2007; Polesel *et al*, 2009). A limited number of studies analysed the relationship between MetS and liver cancer, suggesting a positive association (Russo *et al*, 2008; Inoue *et al*, 2009; Borena *et al*, 2011; Welzel *et al*, 2011), but quantification and particularly the possible relation between MetS and HBV/HCV remain open to discussion.

We provided further results on this issue using data from a multicentric case–control study conducted in Italy. In addition, we explored the association between MetS and HCC risk among subgroups of hepatitis-free and affected subjects.

MATERIALS AND METHODS

Between 1999 and 2002, a case–control study on HCC was carried out in the province of Pordenone (North-eastern Italy) and in the city of Naples (southern Italy) (Talamini *et al*, 2004; Franceschi *et al*, 2006; Montella *et al*, 2011b). Cases were subjects younger than 85 years with incident HCC, admitted to teaching and general hospitals in Pordenone and Naples. Out of the 261 HCC cases satisfying the inclusion criteria, 3 refused the participation, 29 did not supply blood samples, and 44 did not have anthropometric measures at cancer diagnosis. For the remaining 185 cases (median age: 66 years, range: 43–84 years), both questionnaire information and blood samples were available. Most of the HCC cases (78.2%) were histologically or cytologically confirmed; for the remaining cases, cancer diagnosis was based on ultrasound, tomography and elevated α-fetoprotein levels.

Controls were patients younger than 85 years admitted to the same hospitals for a wide spectrum of acute, non-neoplastic conditions. Patients whose hospital admission was due to diseases related to alcohol and tobacco, liver diseases (e.g., hepatitis, cirrhosis, and oesophageal varices) or other chronic diseases, which may have substantially modified their lifestyle, were excluded from the comparison group. Overall, 467 controls were contacted and 462 accepted to participate. Blood samples were available from 431 controls, and 404 provided information on body size (median age: 65 years, range: 40–82 years). Twenty-six per cent of controls were admitted for traumas, 25% for acute surgical conditions, 24% for nontraumatic orthopaedic diseases, 14% for eye diseases, and 10% for other illnesses.

Each case and control provided a 15-ml blood sample the same day of the interview. Sera were screened for antibodies against HCV (anti-HCV) using a third-generation MEIA (AxSYM HCV version 3.0; Abbott Diagnostic Division, Wiesbaden, Germany) and for Hepatitis B surface antigen (HBsAg) using microparticle enzyme immunoassay (AxSYM HBsAg version 2.0; Abbott Diagnostic Division). All study participants signed an informed consent form, according to the recommendations of the Board of Ethics of the National Cancer Institute of Aviano.

Cases and controls were interviewed during their hospital stay using a structured questionnaire including information on socio-demographic characteristics, lifestyle habits (e.g., tobacco smoking and alcohol drinking), usual diet, personal medical history, and family history of cancer. Self-reported information on height and weight at different ages was collected, and body mass index (BMI) was computed according to Quetelet's index (weight/height^2, kg m^{-2}). As information on waist circumference was not available, abdominal obesity was defined using BMI, according to two different thresholds, that is, $\geqslant 25$ and $\geqslant 30$ kg m^{-2}. History of medical conditions, including type-2 diabetes, drug-treated hypertension, and drug-treated or clinical diagnosis of hypercholesterolaemia was self-reported, and included age at first diagnosis. Diseases whose onset was <1 year before hospital admission were not considered.

The indicator of MetS was defined according to the criteria agreed in the 2009 joint interim statement (Alberti *et al*, 2009), adapted to our data, as the presence of at least three components among the following: (1) abdominal obesity, (2) history of a clinical diagnosis or drug-treated hypercholesterolaemia (as a proxy indicator of increased low-density lipoprotein/reduced HDL cholesterol levels), (3) history of drug-treated hypertension (as an alternate indicator of elevated blood pressure), and (4) history of diabetes. We also considered various components of the MetS separately.

Data analysis. Odds ratios (ORs) of HCC, and the corresponding 95% confidence intervals (CIs), for MetS, its components or various combination of components, were derived using unconditional multiple logistic regression models, including terms for centre, sex, age (<55, 55–64, 65–74, $\geqslant 75$ years), education (<7, 7–11, $\geqslant 12$ years), alcohol drinking status (never, ex, current), and maximum lifetime alcohol intake (<21, $\geqslant 21$ drinks per week), smoking habits (never, ex, current: <15 cigarettes per day, current: $\geqslant 15$ cigarettes per day), HBsAg and/or anti-HCV positivity, and non-alcohol energy intake.

RESULTS

Table 1 shows the distribution of 185 cases of HCC and 404 controls according to centre, age, sex, and other covariates. Controls were more often females and were younger than cases. Cases were more likely than controls to have a low level of education, to smoke cigarettes, and to report heavy alcohol drinking; 147 cases (79%) and 44 controls (11%) had serological evidence of chronic infection with HBV and/or HCV.

Table 2 reports the ORs of HCC according to separate and combined components of the MetS. The OR for diabetes was 4.33 (95% CI, 1.89–9.86); no association emerged with treated hypertension and hypercholesterolaemia. The ORs were 1.25 (95% CI, 0.72–2.18) for BMI $\geqslant 25$ kg m^{-2} and 1.97 (95% CI, 1.03–3.79) for BMI $\geqslant 30$ kg m^{-2}. When obesity was defined as BMI $\geqslant 25$ kg m^{-2}, as compared with subjects without any MetS component, the OR was 0.90 (95% CI, 0.47–1.74) for those with one MetS component, and 1.74 (95% CI, 0.82–3.69) for those with $\geqslant 2$ components (P for trend $= 0.149$). The OR for the indicator of MetS was 4.06 (95% CI, 1.33–12.38). When obesity was defined as BMI $\geqslant 30$ kg m^{-2}, the ORs were 1.18 (95% CI, 0.64–2.15) and 3.46 (95% CI, 1.54–7.73) for those with one and $\geqslant 2$ MetS components, respectively (P for trend $= 0.009$). The OR for the presence of the MetS indicator was 1.92 (95% CI, 0.38–9.76).

Table 3 reports results for diabetes and obesity (the only two MetS components associated to HCC risk in our data set), and number of MetS components according to serological evidence of chronic infection with HBV and/or HCV, and in a subset of subjects (11 cases and 216 controls) without markers of chronic

Table 1. Distribution of 185 cases of hepatocellular carcinoma and 404 controls according to selected variables. Italy, 1999–2002

	Cases		Controls	
	N	%	*N*	%
Centre				
Aviano/Pordenone	61	33	224	55
Naples	124	67	180	45
Sex				
Males	149	81	278	69
Females	36	19	126	31
Age (years)				
<55	18	10	83	20
55–64	56	30	115	29
65–74	84	45	144	36
⩾75	27	15	62	15
Education (years)				
<7	126	68	225	56
7–11	45	24	93	23
⩾12	14	8	86	21
Smoking habits				
Never	50	27	134	33
Former	67	36	165	41
Current, cigarettes per day				
1–14	35	19	54	13
⩾15	33	18	51	13
Drinking habits				
Abstainer	16	9	62	15
Current	75	40	302	75
Former	94	51	40	10
Maximal lifetime alcohol intake[a] (drinks per week)				
<21	64	35	186	46
⩾21	105	57	156	39
Non-alcohol energy intake (quartiles[b])				
I	28	15	101	25
II	39	21	101	25
III	51	28	101	25
IV	67	36	101	25
Hepatitis viruses[c]				
No	38	21	360	89
Yes	147	79	44	11

[a]Current and former drinkers combined.
[b]Quartiles were based on the distribution of non-alcohol energy intake among controls only.
[c]Hepatitis was defined as HBsAg and/or anti-HCV positivity.

infection with HBV and/or HCV and with a lifetime alcohol intake <21 drinks per week. Results are given for obesity defined as BMI $\geqslant 30\,kg\,m^{-2}$. Diabetes showed an about three-fold increase in risk of HCC in subjects with and without chronic hepatitis, although the association was significant in the HBsAg− and anti-HCV− group only; obesity and the number of MetS components were associated to HCC in hepatitis-free subjects only, in particular, in those with moderate alcohol consumption.

The combined effect of overweight (i.e., BMI $\geqslant 25\,kg\,m^{-2}$) and diabetes on HCC risk is shown in Figure 1. Compared with the lowest risk category, that is normal-weight subjects without diabetes, the ORs were 1.13 (95% CI, 0.63–2.06) for overweight subjects without diabetes, 4.38 (95% CI, 0.84–22.88) for diabetics of normal weight, and 4.75 (95% CI, 1.75–12.89) for those with both conditions.

DISCUSSION

In this Italian data set, the risk of HCC increased with the number of MetS components, up to an almost four-fold excess risk among subjects with ⩾2 MetS factors, and to over six-fold in subjects without markers of chronic infection with HBV and/or HCV. There was no consistent association in subjects HBsAg+ or anti-HVC+. Metabolic syndrome is a general definition including several factors linked to overweight and hyperinsulinemia. Of these, only diabetes and overweight/obesity were associated to HCC risk in this study, although the relation with BMI was influenced by the threshold chosen. However, inference on hypercholesterolaemia was limited by the availability of information on treated subjects only, who were infrequent in Italy at the time of data collection, and data on hypertension were related to drug-treated hypertension only.

Our results are in broad agreement with previous data on the issue, which showed a positive association of MetS with liver cancer (Russo *et al*, 2008; Inoue *et al*, 2009; Borena *et al*, 2011; Welzel *et al*, 2011). When the single MetS components were analysed separately, overweight/obesity and high blood glucose revealed the strongest associations with liver cancer (Inoue *et al*, 2009; Borena *et al*, 2011).

Of specific interest, we found an association between the number of MetS components and HCC risk only among subjects without markers of chronic infection with HBV and/or HCV. In the Japan Public Health center-based prospective Study Cohort II, MetS increased the risk of HCC also among subjects with HCV infection (Inoue *et al*, 2009). In that study, among the single metabolic factors, only overweight was, however, positively associated to HCC risk in anti-HCV+ subjects. A 14 years follow-up study in Taiwan recruiting 23 820 subjects, for a total of 291 HCC cases, found that obesity (i.e., BMI $\geqslant 30\,kg\,m^{-2}$) and central obesity (i.e., waist circumference >90 in men and >80 in women) were independently associated with a two-fold and a four-fold increased HCC risk among HCV-seropositive subjects, respectively (Chen *et al*, 2008). In the same study, diabetes was associated with a two- to three-fold increased HCC risk, regardless of the presence of chronic infection with hepatitis viruses. However, the risk was highest in HBsAg− and anti-HCV+ subjects (Chen *et al*, 2008).

Diabetes and obesity have been previously related to HCC risk. This study considers the role of their combined effect in the MetS, and their interaction, as well as the modifying effect of HBV and/or HCV on the relation between MetS and liver cancer risk. Diabetes, in fact, has been associated with an about two-fold increased risk of HCC (La Vecchia *et al*, 1994; Adami *et al*, 1996; La Vecchia *et al*, 1997; Wideroff *et al*, 1997; Lagiou *et al*, 2000; El-Serag *et al*, 2004; Yuan *et al*, 2004; Lai *et al*, 2006; Polesel *et al*, 2009; La Vecchia, 2011; Bosetti *et al*, 2012), and precedes the development of both cirrhosis and HCC (Tanaka *et al*, 1997; Dellon and Shaheen, 2005; London and McGlynn, 2006). Insulin resistance has been related to the accumulation of liver fat and to excess cancer risk through the insulin-related growth factors (La Vecchia *et al*, 2011).

Table 2. Distribution of 185 cases of hepatocellular carcinoma and 404 controls, OR and corresponding 95% CI[a], according to separate, combined components and indicators of MetS. Italy, 1999–2002

	All subjects				
	Cases		Controls		
	n	%	*n*	%	OR (95% CI)[a]
Separate components					
Diabetes					
No	148	80	378	94	Ref
Yes	37	20	26	6	4.33 (1.89–9.86)
Treated hypertension					
No	144	78	288	71	Ref
Yes	41	22	116	29	1.13 (0.61–2.09)
Treated hypercholesterolaemia					
No	183	99	380	94	Ref
Yes	2	1	24	6	0.39 (0.05–2.85)
Obesity					
BMI $\geqslant 25\,kg\,m^{-2}$					
No	71	38	146	36	Ref
Yes	114	62	258	64	1.25 (0.72–2.18)
BMI $\geqslant 30\,kg\,m^{-2}$					
No	147	80	323	80	Ref
Yes	38	20	81	20	1.97 (1.03–3.79)
Combined components					
Number of MetS components					
(a) Obesity: BMI $\geqslant 25\,kg\,m^{-2}$					
None	53	29	105	26	Ref
1	80	43	190	47	0.90 (0.47–1.74)
$\geqslant 2$	52	28	109	27	1.74 (0.82–3.69)
P for trend = 0.149					
Increment of 1 MetS component					1.39 (0.99–1.95)
(b) Obesity: BMI $\geqslant 30\,kg\,m^{-2}$					
None	97	52	219	54	Ref
1	62	34	133	33	1.18 (0.64–2.15)
$\geqslant 2$	26	14	52	13	3.46 (1.54–7.73)
P for trend = 0.009					
Increment of 1 MetS component					1.58 (1.12–2.23)
Indicator of MetS[b]					
(a) Obesity: BMI $\geqslant 25\,kg\,m^{-2}$					
No	175	95	388	96	Ref
Yes	10	5	16	4	4.06 (1.33–12.38)
(b) Obesity: BMI $\geqslant 30\,kg\,m^{-2}$					
No	181	98	394	98	Ref
Yes	4	2	10	2	1.92 (0.38–9.76)

Abbreviations: BMI = body mass index; CI = confidence interval; MetS = metabolic syndrome; OR = odds ratio.
[a]Estimated from unconditional logistic regression model adjusted for centre, sex, age, education, drinking status, maximum lifetime alcohol intake, smoking habits, HBsAg and/or anti-HCV positivity, and non-alcohol energy intake.
[b]At least three of the separate components.

With reference to obesity, a meta-analysis, including >6000 cases from 10 cohort studies, showed an 89% excess HCC risk among obese (i.e, BMI, $\geqslant 30\,kg\,m^{-2}$) compared with subjects of normal weight; the pooled relative risk associated to overweight (BMI ranging from 25 to $30\,kg\,m^{-2}$) was 1.17 (95% CI, 1.02–1.34).

The excess risk of liver cancer associated with overweight/obesity and diabetes has been related to the development of non-alcoholic fatty liver disease (NAFLD) (Sanyal *et al*, 2010). NAFLD is characterised by excess fat accumulation in the liver, and ranges from isolated hepatic steatosis to non-alcoholic steatohepatitis (NASH), the more aggressive form of fatty liver disease, which can progress to cirrhosis and HCC (Neuschwander-Tetri and Caldwell, 2003; Larsson and Wolk, 2007; Siegel and Zhu, 2009; Montella *et al*, 2011a). However, NAFLD/NASH increases HCC risk even in the absence of cirrhosis (Ertle *et al*, 2011). Adipose tissue secretes a variety of bioactive hormones, collectively referred to as adipokines, which produce vascular endothelial growth factor, which may contribute to tumour progression (Rega *et al*, 2007). Excess

Table 3. Distribution of 185 hepatocellular carcinoma cases and 404 controls, OR[a] and corresponding 95% CI, according to diabetes and obesity, and number of MetS components, by serological evidence of chronic infection with hepatitis B and/or hepatitis C viruses. Italy, 1999–2002

	HBsAg − and anti-HCV −		HBsAg − and anti-HCV − and lifetime alcohol intake <21 drinks per week		HBsAg + or anti-HCV +	
	Ca:Co	OR (95% CI)[a]	Ca:Co	OR (95% CI)[a]	Ca:Co	OR (95% CI)[a]
Diabetes						
No	29 : 337	Ref	8 : 203	Ref	119 : 41	Ref
Yes	9 : 23	3.65 (1.37–9.75)	3 : 13	9.14 (1.39–60.29)	28 : 3	2.57 (0.61–10.64)
Obesity[b]						
No	22 : 288	Ref	7 : 170	Ref	125 : 35	Ref
Yes	16 : 72	3.32 (1.51–7.32)	4 : 46	2.69 (0.61–11.90)	22 : 9	0.69 (0.21–2.27)
Number of MetS components						
0	12 : 197	Ref	2 : 112	Ref	85 : 22	Ref
1	12 : 116	1.76 (0.70–4.45)	5 : 74	7.40 (0.90–61.10)	50 : 17	0.90 (0.35–2.31)
⩾2	14 : 47	6.45 (2.35–17.75)	4 : 30	20.21 (1.96–208.49)	12 : 5	0.69 (0.15–2.99)
P for trend	*<0.001*		*0.009*			*0.612*
Increment of 1 MetS component	2.16 (1.38–3.39)		3.41 (1.31–8.89)		0.84 (0.46–1.52)	

Abbreviations: Ca = cases; CI = confidence interval; Co = controls; HCV = hepatitis C virus; HBsAg = hepatitis B surface antigen; MetS = metabolic syndrome; OR = odds ratio.
[a]Estimated from unconditional logistic regression model adjusted for centre, sex, age, education, drinking status (when appropriate), maximum lifetime alcohol intake (when appropriate), smoking habits, and non-alcohol energy intake.
[b]Obesity was defined as body mass index (BMI) $\geqslant 30\,kg\,m^{-2}$.

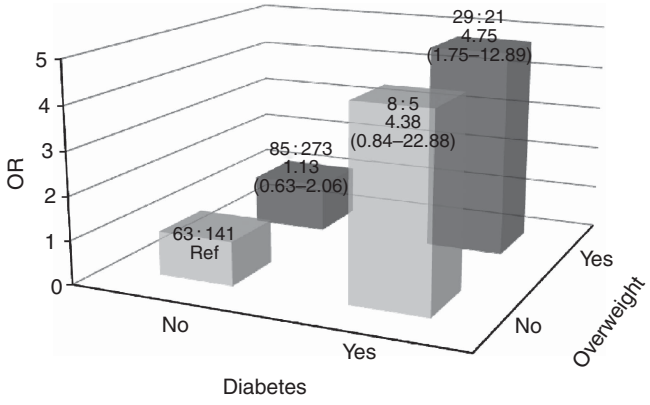

Figure 1. Distribution of 185 hepatocellular carcinoma cases and 404 controls, odds ratios (OR) and 95% confidence intervals (CIs) according to the combination of diabetes and overweight. Italy, 1999–2002. ORs were estimated from unconditional logistic regression model adjusted for centre, sex, age, education, drinking status, maximum lifetime alcohol intake, smoking habits, HBsAg and/or anti-HCV positivity, and non-alcohol energy intake. Overweight was defined as BMI $\geqslant 25\,kg\,m^{-2}$.

intracellular fatty acids, adenosine triphosphate depletion, oxidant stress, and mitochondrial dysfunction may cause hepatocellular injuries in the steatotic liver (Neuschwander-Tetri and Caldwell, 2003).

To limit possible sources of bias, we included in the control group subjects admitted for a wide spectrum of acute, non-neoplastic conditions, unrelated to the major risk factors for HCC. The practically complete participation rate and the comparable catchment areas of cases and controls contributed to reduce any potential selection bias. Cases may recall history of disease more frequently than controls. However, the hospital setting should have improved the comparability of information, as cases and controls are interviewed under similar conditions (Breslow and Day, 1980).

Among limitations, information on MetS components was based on self-reported data from a questionnaire, which collected history of diabetes, treated hypertension, and treated hyperlipidaemia, rather than direct measurements of fasting plasma glucose, blood pressure, triglycerides and HDL cholesterol. Underestimation of the prevalence of MetS may therefore have occurred. However, data on diabetes collected on our questionnaire were satisfactorily reliable, with a k statistic of 0.85 from almost 300 subjects interviewed twice (Bosetti *et al*, 2001). Moreover, a recent cohort study from Spain showed that self-declared data on the criteria of MetS and on MetS itself are sufficiently accurate for epidemiological inference (Barrio-Lopez *et al*, 2011). Validation studies of hypertension confirmed with a medical examination found a reasonable accuracy of self-reported information; a somewhat lower validity was usually found for self-reported hypercholesterolaemia (Colditz *et al*, 1986; Giles *et al*, 1995; Vargas *et al*, 1997; Martin *et al*, 2000). Weight also was self-reported and possibly underestimated, particularly in overweight and obese subjects (Stark *et al*, 1981; Stewart, 1982; Millar, 1986). However, such information bias is likely to be similar for cases and controls, and, consequently, should have led to an attenuation of the real association (Breslow and Day, 1980). In addition, information on presence of fatty liver/NAFLD/NASH was not available in our study.

Another possible limitation is the use of BMI as a proxy of waist circumference in defining people with central obesity. However, the World Health Organization, in its formulation of MetS diagnostic criteria, considered BMI as a valid proxy of waist-to-hip ratio (Alberti *et al*, 2006). In our analyses, abdominal obesity was defined as either BMI $\geqslant 25$ or BMI $\geqslant 30\,kg\,m^{-2}$, and the excess risk associated to the MetS persisted even when the lower threshold was considered. We used one of the possible MetS definition proposed in the literature (Alberti *et al*, 2009). When the presence of MetS was defined according to the International Diabetes Federation criteria (Third Report of the NCEP Expert Panel, 2002) (adapted to our data) as the presence of central obesity plus at least two other components, the OR for the

indicator of MetS did not substantially change (OR = 2.12, 95% CI, 0.40–11.26, with obesity defined as BMI $\geqslant 30\,kg\,m^{-2}$; OR = 4.36, 95% CI, 1.40–13.56, with obesity defined as BMI $\geqslant 25\,kg\,m^{-2}$).

The different prevalence of chronic hepatitis infection with HBV/HCV between HCC cases and controls, and the relatively low prevalence of obesity (i.e., BMI $\geqslant 30\,kg\,m^{-2}$) and other MetS components in our study sample, limited our results on these associations, particularly in subgroup analyses. In light of these considerations, caution in interpreting these results is needed.

Concerning confounding, the associations persisted after adjustment for the main recognised HCC risk factors, including chronic infection with HBV/HCV, tobacco smoking, and alcohol drinking.

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