Metabolic syndrome and hepatocellular carcinoma risk

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Background: Hepatocellular carcinoma (HCC) has been associated with 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) ≥ 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 ≥ 25, and 1.92 (95% CI, 0.38–9.76) defining it as BMI ≥ 30. The risk increased with the number of MetS components, up to an almost four-fold excess risk among subjects with ≥ 2 MetS factors. Among subjects without chronic infection with hepatitis B and/or C, the OR for those with ≥ 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
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 consent form, according to the recommendations of the Board of Ethics of the National Cancer Institute of Aviano.

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.

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 $\geq 25$ kg m$^{-2}$ and 1.97 (95% CI, 1.03–3.79) for BMI $\geq 30$ kg m$^{-2}$. When obesity was defined as BMI $\geq 25$ 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 $\geq 2$ 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 $\geq 30$ 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 $\geq 2$ 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
infection with HBV and/or HCV and with a lifetime alcohol intake < 21 drinks per week. Results are given for obesity defined as BMI ≥ 25 kg m⁻². Diabetes showed an about two-fold increase in risk of HCC in hepatitis-free subjects only, in particular, in those with moderate alcohol consumption.

The combined effect of overweight (i.e., BMI ≥ 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-HCV +. 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 ≥ 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; Iagiu 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 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* (drinks per week) |
| < 21 | 64 | 35 | 186 | 46 |
| ≥ 21 | 105 | 57 | 156 | 39 |
| Non-alcohol energy intake (quartilesb) |
| I | 28 | 15 | 101 | 25 |
| II | 39 | 21 | 101 | 25 |
| III | 51 | 28 | 101 | 25 |
| IV | 67 | 36 | 101 | 25 |
| Hepatitis viruses |
| No | 38 | 21 | 360 | 89 |
| Yes | 147 | 79 | 44 | 11 |

*aCurrent and former drinkers combined.

bQuartiles were based on the distribution of non-alcohol energy intake among controls only.

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With reference to obesity, a meta-analysis, including 4600 cases from 10 cohort studies, showed an 89% excess HCC risk among obese (i.e., BMI, $\geq 30$ 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 2. Distribution of 185 cases of hepatocellular carcinoma and 404 controls, OR and corresponding 95% CI, according to separate, combined components and indicators of MetS. Italy, 1999–2002 |
|-------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Separate components                             |                                 |                                 |                                 |                                 |                                 |
| Diabetes                                        |                                 |                                 |                                 |                                 |                                 |
| No                                                                  | Yes                             |                                 |                                 |                                 |                                 |
| n         | %                | n         | %                | OR (95% CI)a                    |                                 |
| 148       | 80                | 378       | 26               | Ref                             | 4.33 (1.89–9.86)                |
| Treated hypertension                            |                                 |                                 |                                 |                                 |                                 |
| No                                                                  | Yes                             |                                 |                                 |                                 |                                 |
| n         | %                | n         | %                | OR (95% CI)a                    |                                 |
| 144       | 78                | 283       | 116              | Ref                             | 1.13 (0.61–2.09)                |
| Treated hypercholesterolaemia                    |                                 |                                 |                                 |                                 |                                 |
| No                                                                  | Yes                             |                                 |                                 |                                 |                                 |
| n         | %                | n         | %                | OR (95% CI)a                    |                                 |
| 183       | 99                | 380       | 24               | Ref                             | 0.39 (0.05–2.85)                |
| Obesity                                          |                                 |                                 |                                 |                                 |                                 |
| BMI $\geq 25$ kg m$^{-2}$                        |                                 |                                 |                                 |                                 |                                 |
| No                                                                  | Yes                             |                                 |                                 |                                 |                                 |
| n         | %                | n         | %                | OR (95% CI)a                    |                                 |
| 71        | 38                | 146       | 258              | Ref                             | 1.25 (0.72–2.18)                |
| BMI $\geq 30$ kg m$^{-2}$                        |                                 |                                 |                                 |                                 |                                 |
| No                                                                  | Yes                             |                                 |                                 |                                 |                                 |
| n         | %                | n         | %                | OR (95% CI)a                    |                                 |
| 147       | 80                | 323       | 81               | Ref                             | 1.97 (1.03–3.79)                |
| Combined components                              |                                 |                                 |                                 |                                 |                                 |
| Number of MetS components                        |                                 |                                 |                                 |                                 |                                 |
| (a) Obesity: BMI $\geq 25$ kg m$^{-2}$            |                                 |                                 |                                 |                                 |                                 |
| None                                                               | 1 $> 2$                         |                                |                                |                                |                                |
| n         | %                | n         | %                | OR (95% CI)a                    |                                 |
| 53        | 29                | 105       | 26               | Ref                             | 0.90 (0.47–1.74)                |
| (b) Obesity: BMI $\geq 30$ kg m$^{-2}$            |                                 |                                 |                                 |                                 |                                 |
| None                                                               | 1 $> 2$                         |                                |                                |                                |                                |
| n         | %                | n         | %                | OR (95% CI)a                    |                                 |
| 97        | 52                | 219       | 54               | Ref                             | 1.18 (0.64–2.15)                |
| Indicator of MetSb                                               |                                 |                                 |                                 |                                 |                                 |
| (a) Obesity: BMI $\geq 25$ kg m$^{-2}$            |                                 |                                 |                                 |                                 |                                 |
| No                                                                  | Yes                             |                                 |                                 |                                 |                                 |
| n         | %                | n         | %                | OR (95% CI)a                    |                                 |
| 175       | 95                | 388       | 16               | Ref                             | 4.06 (1.33–12.38)               |
| (b) Obesity: BMI $\geq 30$ kg m$^{-2}$            |                                 |                                 |                                 |                                 |                                 |
| No                                                                  | Yes                             |                                 |                                 |                                 |                                 |
| n         | %                | n         | %                | OR (95% CI)a                    |                                 |
| 181       | 98                | 394       | 10               | Ref                             | 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.
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 (Goldtz 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.

Figure 1. Distribution of 185 hepatocellular carcinoma cases and 404 controls, OR* and corresponding 95% CI, according to diabetes and overweight, and number of MetS components, by serological evidence of chronic infection with hepatitis B and/or hepatitis C viruses. Italy, 1999–2002

Table 3. Distribution of 185 hepatocellular carcinoma cases and 404 controls, OR 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)     | Ca:Co OR (95% CI)                                                  | Ca:Co OR (95% CI)   |
| Diabetes         |                       |                                                                     |                     |
| No               | 29:337                | 119:41                                                             | 8:203               |
| Yes              | 9:23                  | 3.65 (1.37–9.75)                                                   | 9.14 (1.39–60.29)   |
| Obesityb         |                       |                                                                     |                     |
| No               | 22:288                | 7:170                                                              | 125:35              |
| Yes              | 16:72                 | 3.32 (1.51–7.32)                                                   | 2.69 (0.61–11.90)   |
| Number of MetS components |                |                                                                     |                     |
| 0                | 12:197                | 85:22                                                              | 4.67 (0.90–61.10)   |
| 1                | 12:116                | 5:74                                                               | 20.21 (1.96–208.49) |
| ≥2               | 14:47                 | 4:30                                                               | 12:5                |
| P for trend      | <0.001                | 0.009                                                              | 0.69 (0.15–2.99)    |
| 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:Co = cases: controls; CI = confidence interval; HCV = hepatitis C virus; HBsAg = hepatitis B surface antigen; MetS = metabolic syndrome; OR = odds ratio.

*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.

bObesity was defined as body mass index (BMI) ≥25 kg m–2.
indicator of MetS did not substantially change (OR = 2.12, 95% CI, 0.40–11.26, with obesity defined as BMI ≥ 30 kg m⁻²; OR = 4.36, 95% CI, 1.40–13.56, with obesity defined as BMI ≥ 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 ≥ 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 recognized HCC risk factors, including chronic infection with HBV/HCV, tobacco smoking, and alcohol drinking.

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