Prevalence of type 2 diabetes mellitus in Japanese patients with hepatocellular carcinoma

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Abstract. The possibility has been raised in a number of cohort and case-control studies that diabetes mellitus (DM) may increase the risk of liver cancer, as well as that of cancer at other sites. To verify this possibility, we conducted a retrospective cohort study to determine the prevalence of type 2 DM in Japanese patients with hepatocellular carcinoma (HCC). A total of 1,251 patients with HCC, diagnosed at two major liver centers in the Nagasaki area, were consecutively recruited and categorized according to the etiology of HCC into four groups: HCC-B, HCC-C, HCC-BC and HCC-nonBC cases. Type 2 DM was diagnosed on the basis of standard criteria. The prevalence rate of HCC-nonBC and HCC-C was significantly higher than that of HCC-B, while the prevalence rate of HCC-nonBC was significantly higher than that of HCC-C. The prevalence of type 2 DM in HCC-B, HCC-C and HCC-nonBC patients under 66 years of age was 11, 31 and 32%, respectively, vs. 24, 22 and 40%, respectively, in patients over 66 years of age. In patients over 66 years of age, the prevalence of type 2 DM in HCC-B and HCC-nonBC cases was increased, whereas the prevalence of type 2 DM in HCC-C cases was significantly decreased. Our findings indicate that the effects of the interaction between type 2 DM and HCV increase the prevalence of HCC.

Introduction

Of the three leading causes of death in Japan – malignant neoplasms, cardiovascular diseases and cerebrovascular diseases – malignant neoplasms have been the leading cause of death in Japan since 1981. For the last 30 years, liver cancer has been the third leading cause of death by malignant neoplasms in men and, during the past decade, has ranked fifth in women (1-3). Hepatocellular carcinoma (HCC) accounts for 85-90% of cases of primary liver cancer, and chronic hepatitis B and C infections are the main cause of HCC. However, the prevalence of HCC in Japan in the liver of patients that are both hepatitis B surface antigen (HBsAg)- and hepatitis C virus (HCV)-RNA-negative has been increasing over the last 12 years (4).

Epidemiological findings have recently been reported proposing a link between type 2 diabetes mellitus (DM) and cancer in various organs (5,6). The possibility that DM may increase the risk of liver cancer, as well as cancer at other sites, has been raised in a number of cohorts and case-control studies (7-10). We carried out this retrospective study to determine the prevalence of type 2 DM in Japanese patients with HCC.

Patients and methods

Patients. A total of 1,251 patients with HCC diagnosed between January 1991 and December 2005 at the liver disease centers of the National Nagasaki Medical Center and Nagasaki University Hospital were consecutively recruited for this study. Informed consent was obtained from all patients. The diagnosis of HCC was based on the elevation of serum α-fetoprotein or des-γ-carboxy prothrombin levels, characteristic image findings obtained using ultrasonography, computerized tomography, magnetic resonance imaging and hepatic angiography, and/or histological diagnosis using tumor biopsy samples.

Etiology of HCC. The HCC cases were categorized according to etiology into four groups: HCC-B, hepatitis B virus surface antigen (HBsAg)-positive and hepatitis C virus (HCV)-RNA-negative; HCC-C, HCV-RNA-positive and HBsAg-negative; HCC-BC, both HBsAg- and HCV-RNA-positive; and HCC-nonBC, both HBsAg- and HCV-RNA-negative. A diagnosis of chronic HCV infection was based on the presence of both serum anti-HCV antibody and HCV-RNA detected by polymerase chain reaction (PCR), while a diagnosis of chronic hepatitis B virus (HBV) infection was based on the presence of HBsAg.

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Table I. Characteristics of the HCC patients.

	HCC-B	HCC-C	HCC-BC	HCC-nonBC	Total
No.	248	809	29	165	1,251
Gender					
Male	191	566	19	121	897
Female	57	243	10	44	354
Ratio (male/female)	3.4	2.3	1.9	2.8	2.5
Age (IQR), in years	57 (15)	67 (9)	65 (12)	67 (14)	66 (11)
<66	190	341	17	71	619
≥66	58	468	12	94	632
Child-Pugh grade					
A	95	70	80	67	412
B	111	213	240	292	1,134
C	8	8	9	11	46

Gender: HCC-B vs. HCC-C, p=0.031. Age: HCC-B vs. HCC-C, p<0.001; HCC-B vs. HCC-BC, p=0.022; HCC-B vs. HCC-nonBC, p<0.0001; HCC-C vs. HCC-BC, p=0.004; HCC-BC vs. HCC-nonBC, p=0.009. IQR, interquartile range.

Diagnosis of type 2 DM. Type 2 DM was diagnosed on the basis of the presence of hyperglycemia (≥200 mg/dl) in at least two postabsorptive samples, overt glycosuria, or both; or active treatment with insulin, oral hypoglycemic agents, or both. No consideration was given to minor alterations in glucose metabolism, such as impaired glucose tolerance based on an oral glucose tolerance test, in accordanc with World Health Organization criteria.

Statistical analysis. Data were analyzed by the Mann-Whitney U test for continuous ordinal data, and by the χ^2 test with Yates' correction and Fisher's exact test for associations between two qualitative variables. p<0.05 was considered statistically significant. Data analysis was performed with SPSS version 16.0 for Windows.

Results

Clinical features of the studied patients. As shown in Table I, of the 1,251 patients with HCC, 20% (248/1,251) were diagnosed with HCC-B, whereas 65% (809/1,251) had HCC-C and an additional 2% (29/1,251) had HCC associated with both viruses. In the remaining 165 patients (13%), no association was found between HCC and either of the viruses. Analyzing the patients with HCC by category revealed the male/female ratio in HCC-B, HCC-C, HCC-BC and HCC-nonBC to be 3.4, 2.3, 1.9 and 2.8, respectively. The male/female ratio in HCC-C was less than that in HCC-B. In addition, the median age of patients diagnosed with HCC-B, HCC-C, HCC-BC and HCC-nonBC was 57, 67, 65 and 67 years, respectively. The median age of patients diagnosed with HCC-B was significantly lower than that of the patients with other types of HCC. Among the patients with HCC, 25% (310/1,251) had type 2 DM, 3% (34/1,251) HCC-B, 16% (209/1,251) HCC-C, 1% (6/1,251) HCC-BC and 5% (61/1,251) HCC-nonBC.

Prevalence of type 2 DM by stratification according to etiology in patients with HCC. Cohorts of patients with HCC were divided according to etiology. Fig. 1 shows that the prevalence rate of type 2 DM in HCC-B, HCC-C, HCC-BC and HCC-nonBC was 14% (34/248), 26% (209/809), 37% (61/165) and 21% (6/29), respectively. The prevalence rate of HCC-nonBC and HCC-C was significantly higher than that of HCC-B (HCC-B vs. HCC-nonBC, p≤0.001; HCC-B vs. HCC-C, p≤0.001), while the prevalence rate of HCC-nonBC was significantly higher than that of HCC-C (HCC-C vs. HCC-nonBC, p=0.003).

The prevalence rate of type 2 DM was 25% in patients under 66 years of age (154/619) and 25% in patients over 66 years of age (156/632). Fig. 2 shows the age distribution of the prevalence rate for type 2 DM in HCC-B, HCC-C and HCC-nonBC cases. The prevalence rate of type 2 DM in HCC-B, HCC-C and HCC-nonBC was 11% (20/190), 31% (107/341) and 32% (23/71), respectively, in patients under 66 years of age, vs. 24% (14/58), 22% (102/468) and 40% (38/94), respectively, for those over 66 years of age. The prevalence rate of type 2 DM in HCC-B and HCC-nonBC patients over 66 years of age was increased, whereas that of HCC-C was significantly decreased.

Discussion

A nationwide health survey regarding the prevalence of DM in the general Japanese population conducted in 2006 indicated that the prevalence of DM in Japan was 12%. However, the prevalence rate of type 2 DM is higher in patients with HCC than in the general Japanese population. In this two major liver center-based cohort study designed to examine the prevalence of type 2 DM in HCC patients, 25% of patients with HCC had type 2 DM. Previous studies have suggested that DM is a potential risk factor for HCC (10-13). Inoue *et al* prospectively
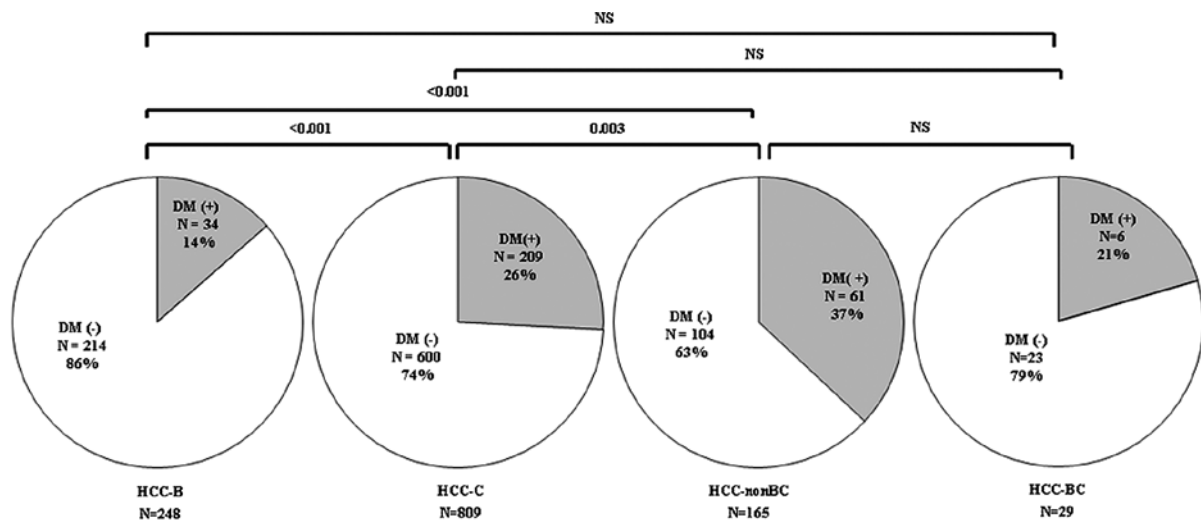
Figure 1. Prevalence rate of type 2 DM in HCC-B, HCC-C, HCC-BC and HCC-nonBC.

examined the association between a history of DM and the subsequent risk of cancer in a Japan Public Health Center-based prospective study, and found an increased risk of liver cancer in DM patients (12).

The present study found that the prevalence of type 2 DM was significantly higher in HCC-nonBC than in HCC-B and HCC-C patients. In particular, type 2 DM persisted in patients without chronic hepatitis virus infections; type 2 DM in these individuals may explain a relevant proportion of the observed cases of HCC. Previous studies have suggested that diabetes and/or non-alcoholic fatty liver disease account for at least a portion of these 'idiopathic' cases (14-16). Findings from the present study support the hypothesis that the presence of DM alone accounts for approximately 37% of cases of HCC-nonBC.

Investigations into the possible biological mechanisms of the association between type 2 DM and HCC-nonBC have been site-specific. However, these associations may be the result of metabolic and hormonal aberrations associated with type 2 DM, and common biological mechanisms may be at least partially associated with insulin and insulin-like growth factors (IGFs) (17).

The most obvious change in diabetic patients is reduced insulin sensitivity with compensatory hyperinsulinemia and elevated levels of IGF-1, which may in turn stimulate cell proliferation in the liver (18,19). At the same time, insulin activates the IGF-1 receptor, which is known to have a growth-promoting effect, including the modulation of cell cycle progression. Excess insulin may also indirectly affect the development of cancer by down-regulating the level of IGF-binding protein 1, which increases the level and bioavailability of total circulating IGF-1. Obesity and physical inactivity also cause hyperinsulinemia, and are thus also ultimately associated with cancer (17-20).

A survey of HCC-nonBC conducted between 1995 and 2003 in Japan by the Inuyama Hepatitis Research Group found that individuals with HCC-nonBC accounted for 9.3% of the general population (2). In the present study, we found the percentage of HCC-nonBC to be 14.1% in the Nagasaki area. Furthermore, the number and proportion of HCC-nonBC
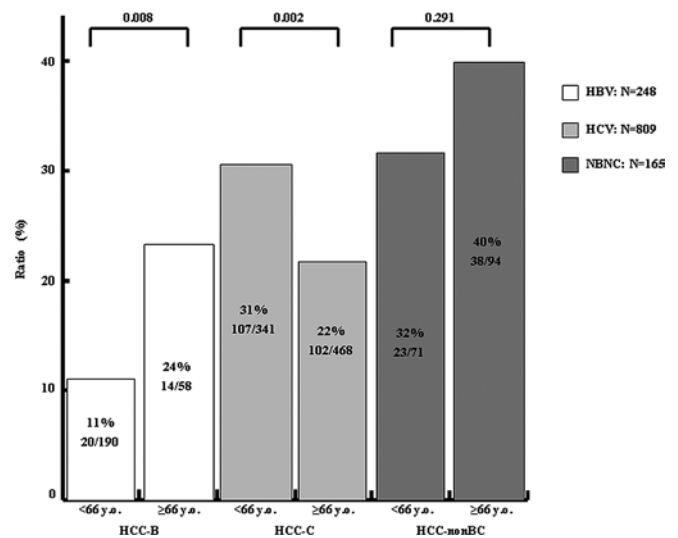

Figure 2. Age distribution for the prevalence rate of type 2 DM in HCC-B, HCC-C and HCC-nonBC.

cases gradually increased from 1981 to 2005 (4). According to an epidemiological study on DM by Nakano et al, the number of patients with DM has been gradually increasing since the development of an automotive society and the Westernization of the Japanese diet (21). Since the prevalence of DM increases with age, the proportion of individuals with DM aged 60 or above has exceeded two-thirds of the estimated total number of patients in Japan (7.40 million in 2002), which has a rapidly aging society (21). In other words, the number of individuals with type 2 DM is increasing in Japan, and these individuals are at high risk for HCC. Thus, the number of HCC-nonBC cases will increase in the next decade in Japan.

Approximately 60% of liver cancer cases in Japan are anti-HCV-positive (4). An experimental study revealed that HCV infection itself induces insulin resistance through the disturbance of the insulin intracellular signaling pathway by the hepatitis virus core protein (22). Liver fat deposition may contribute to insulin resistance, which in turn leads to a loss of the restraining effect of insulin on the production of glucose

by hepatocytes, thereby causing diabetes (23). Steatosis occurs more frequently in patients with chronic HCV infection than in those with chronic HBV infection; this may explain the increased risk of DM among HCV patients (24). Although we proposed possible explanations for the correlation between HCV infection and the prevalence rate of type 2 DM in patients in this study, it is also possible that the mechanism is multifactorial. A previous study identified chronic hepatitis B as having no relationship to DM, and on the basis of the results of this study, we arrive at the same conclusion (25,26).

Several studies have indicated that the progression from chronic hepatitis to cirrhosis and HCC is accelerated by dual HCV infection (11,27). The strong effect of DM on HCC in the absence of hepatitis infection suggests that, in addition to the hepatitis C causal pathway, HCC is mediated through the reduction of IGF-1 factors or IGF binding protein-3, caused by hyperinsulinemia. This in turn stimulates the proliferation of cancer cells, as demonstrated by Lagiou *et al* (28). In the present study, the prevalence rate of DM in patients with HCC-C was significantly higher in patients older than 66 years of age. Our findings demonstrate that the effects of the interaction between DM and HCV further the incidence of HCC.

In conclusion, the prevalence of HCC-nonBC and HCC-C was significantly higher than that of HCC-B, while the prevalence of HCC-nonBC was significantly higher than that of HCC-C. In patients over 66 years of age, the prevalence of type 2 DM in HCC-B and HCC-nonBC cases was increased, whereas the prevalence of type 2 DM in HCC-C cases was significantly decreased. Our findings indicate that the interaction between type 2 DM and HCV increases the prevalence of HCC.

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