Table 2 Hazard ratios (HRs) and 95% CIs of hepatocellular carcinoma according to the metabolic factors[a]

	Number of subjects	Number of cases	Person-years	HR	(CI)
Components of metabolic factors					
High blood pressure					
Absent	7,156	35	90,694	1.00	
Present	10,434	67	132,107	0.97	(0.62–1.53)
High glucose					
Absent	13,950	65	177,493	1.00	
Present	3,640	37	45,307	1.75	(1.11–2.74)
Low HDL-cholesterol					
Absent	13,487	70	170,673	1.00	
Present	4,103	32	52,128	1.17	(0.72–1.92)
High triglycerides					
Absent	13,442	87	170,277	1.00	
Present	4,148	15	52,523	0.75	(0.40–1.39)
Overweight					
Absent	12,180	64	153,362	1.00	
Present	5,410	38	69,438	2.22	(1.42–3.48)
Metabolic factors in the aggregate					
≥3 factors					
Absent	13,692	73	173,316	1.00	
Present	3,898	29	49,485	1.68	(1.06–2.66)
≥2 factors in addition to being overweight					
Absent	14,756	81	186,608	1.00	
Present	2,834	21	36,192	2.14	(1.27–3.61)

[a] Model includes gender (stratified, men and women combined only), age (stratified, 5-year age categories), area (stratified, 6 PHC areas), smoking status (never, past, current), weekly ethanol intake (past, never, <weekly, <150 g per week, 150 to <300 g per week, ≥300 g per week), coffee intake (never, 1–2 days/week, 3–4 days/week, everyday (1–2 cups/day, ≥3 cups/day), total cholesterol (mg/dl, continuous) and HCV infection status (anti-HCV antibody negative, positive) and HBV infection status (HbsAg negative, positive) and individual components of metabolic syndrome, namely, high blood pressure, high glucose, low HDL-cholesterol, high triglycerides, and overweight (yes, no)

metabolic factors on HCC were overweight and a high glucose state.

Previous epidemiological observations on the effect of metabolic factors in the aggregate on the risk of HCC are scarce [9, 10]. Results have generally shown positive association with metabolic factors in the aggregate, although one [9] did not account for hepatitis virus infection status, and another [10] lacked information on some of the components of metabolic factors and provided results only for subjects without infection. Meanwhile, a number of epidemiological studies have implicated diabetes as a risk factor for HCC [4, 10–20]. Obesity is the most important risk factor for diabetes, and diabetes and obesity are highly related events [37]. A number of epidemiological studies have reported an association between obesity and HCC [10, 21–26], most of which found a significant positive association in men but a weaker positive association in women. The only two studies accounting for hepatitis virus infection status found a significant positive association among those with HCV infection [10, 21], albeit that results for men and women were combined.

The biological mechanism by which metabolic factors leads to HCC has not been fully clarified. One suggested candidate is that obesity leads to insulin resistance and steatosis, which are associated with the release of inflammatory mediators such as tumor necrosis factor (TNF)-α in the liver. This would in turn enhance the production of cytokines, including interleukin (IL)-6 and IL-8, leading to steatohepatitis or NASH [15]. On this basis, obesity and diabetes cause hepatic inflammation, leading to oxidative stress and lipid peroxidation, subsequently resulting in hepatic injury, fibrosis, and eventual cirrhosis and HCC [37]. Several studies have also suggested a synergistic effect of diabetes with viral hepatitis [20] and alcohol intake [15, 16, 20].

It is also known that the liver plays a key role in serum lipoprotein synthesis and metabolism, and impaired lipid metabolism is often found in patients with chronic liver diseases [38]. This finding is supported by several cross-sectional studies among HCV-positive subjects [39, 40]. With metabolic syndrome, free fatty acids (FFAs) are released in abundance from an expanded adipose tissue

Table 3 Hazard ratios and 95% CIs of hepatocellular carcinoma according to metabolic factors by hepatitis viral infection status[a]

	HCV-antibody positive subjects					HCV-antibody and HBsAg negative subjects				
	Number of subjects	Number of cases	Person-years	HR	(CI)	Number of subjects	Number of cases	Person-years	HR	(CI)
Components of metabolic factors										
High blood pressure										
Absent	346	26	4,113.2	1.00		6,650	7	84,548.0	1.00	
Present	612	47	7,142.0	0.98	(0.56–1.72)	9,563	11	121,691.1	0.60	(0.21–1.70)
High glucose										
Absent	730	48	8,678.0	1.00		12,889	10	164,622.3	1.00	
Present	228	25	2,577.2	1.49	(0.85–2.61)	3,324	8	41,616.8	2.48	(0.93–6.60)
Low HDL-cholesterol										
Absent	705	48	8,346.6	1.00		12,445	14	158,055.8	1.00	
Present	253	25	2,908.6	1.18	(0.65–2.16)	3,768	4	48,183.3	0.63	(0.18–2.17)
High triglycerides										
Absent	779	63	9,117.6	1.00		12,307	13	156,661.8	1.00	
Present	179	10	2,137.6	0.64	(0.30–1.39)	3,906	5	49,577.3	2.14	(0.64–7.18)
Overweight										
Absent	706	44	8,335.5	1.00		141,479	11	11,883.0	1.00	
Present	252	29	2,919.7	2.66	(1.54–4.62)	64,760	7	4,678.5	1.81	(0.64–5.07)
Metabolic factors in the aggregate										
≥3 factors										
Absent	753	51	8,850.8	1.00		12,596	12	160,133.1	1.00	
Present	205	22	2,404.4	1.83	(1.05–3.18)	3,617	6	46,106.0	1.80	(0.65–4.98)
≥2 factors in addition to being overweight										
Absent	826	57	9,710.2	1.00		13,556	14	172,296.2	1.00	
Present	132	16	1,545.0	2.57	(1.37–4.80)	2,647	4	33,942.9	1.79	(0.57–5.63)

[a] Model includes gender (stratified, men and women combined only), age (stratified, 5-year age categories), area (stratified, 6 PHC areas), smoking status (never, past, current), weekly ethanol intake (past, never, <weekly, <150 g per week, 150–<300 g per week, ≥300 g per week), coffee intake (never, 1–2 days/week, 3–4 days/week, everyday (1–2 cups/day, ≥3 cups/day), total cholesterol (mg/dl, continuous) and HCV infection status (anti-HCV antibody negative, positive) and HBV infection status (HbsAg negative, positive) and individual components of metabolic syndrome, namely, high blood pressure, high glucose, low HDL-cholesterol, high triglycerides, and overweight (yes, no)

Table 4 Hazard ratios and 95% CIs of hepatocellular carcinoma according to body mass index and glucose level status[a]

		Total subjects					HCV-antibody positive subjects					HCV-antibody and HBsAg negative subjects				
		Number of subjects	Number of cases	Person-years	HR	(CI)	Number of subjects	Number of cases	Person-years	HR[a]	(CI)	Number of subjects	Number of cases	Person-years	HR	(CI)
Body mass index																
<25		12,180	64	153,362.4	1.00		704	44	8,335.5	1.00		11,193	11	141,479.4	1.00	
25 to <27		2,903	21	37,183.2	2.07	(1.22–3.52)	150	16	1,690.6	2.55	(1.34–4.85)	2,684	4	34,619.2	1.91	(0.59–6.14)
≥27		2,507	17	32,255.0	2.72	(1.51–4.89)	102	13	1,229.1	3.08	(1.51–6.30)	2,336	3	30,140.5	1.84	(0.48–7.04)
p for trend					*0.019*					*0.017*					0.414	
Overweight	High glucose															
Absent	Absent	9,874	43	124,802.5	1.00		550	29	6,549.6	1.00		9,101	8	115,441.0	1.00	
Absent	Present	2,306	21	52,690.9	1.57	(0.88–2.79)	156	15	1,785.9	1.75	(0.86–3.58)	2,092	3	26,038.4	1.14	(0.28–4.62)
Present	Absent	4,076	22	28,559.9	2.01	(1.16–3.49)	180	19	2,128.4	3.06	(1.59–5.88)	3,788	2	49,181.3	0.77	(0.16–3.69)
Present	Present	1,334	16	16,747.3	4.10	(2.19–7.69)	72	10	791.3	3.36	(1.47–7.68)	1,232	5	15,578.4	5.14	(1.60–16.55)
p for interaction between high glucose and overweight					*0.620*					*0.369*					*0.121*	

[a] Adjusted for age (stratified, 5-year age categories), area (stratified, 6 PHC areas), smoking status (never, past, current), weekly ethanol intake (past, never, <weekly, <150 g per week, 150 to <300 g per week, ≥300 g per week), coffee intake (never, 1–2 days/week, 3-4 days/week, everyday (1–2 cups/day, ≥3 cups/day), total cholesterol (mg/dl, continuous), and HCV infection status (anti-HCV antibody-negative, -positive) and HBV infection status (HBsAg-negative, -positive)

mass. In the liver, FFAs produce an increased production of glucose, triglycerides, and secretion of very low density lipoproteins (VLDL), with lipid/lipoprotein abnormalities such as reductions in HDL-cholesterol and an increased density of low density lipoprotein (LDL) [8]. This VLDL secretion and fatty acid β-oxidation, may in turn, result in increased triglyceride synthesis in the liver [41, 42]. A similar mechanism may also be involved in the association between metabolic factors and HCC. In this study, however, the positive association between low HDL-cholesterol and risk of HCC was not significant.

Based on this study, we speculate that metabolic factors may affect the risk of HCC not only in those with hepatitis virus infection but also without hepatitis virus infection, via a common or different pathway. More specifically, metabolic factors may play a role in those without hepatitis virus infection through NASH/NAFLD and related conditions, and in promoting carcinogenesis after infection. Nevertheless, our analyses among both HCV- and HBV infection-negative subjects were based on a small number of cases, meaning no definite conclusions can be drawn, and any interpretation requires caution. In addition, clinical investigations have shown that most HCC in this population originates from HCV- or HBV infection [7], and that the proportion of non-B/non-C HCC in all HCC has been reported to be around 10–12% since 1999 [43]. In addition, a small proportion of NAFLD/NASH patients develop HCC [44]. Together, these findings imply that the contribution of factors other than hepatitis virus infection such as NASH/NAFLD in this population may not be large, at the present time at least. However, given the increasing trend in the incidence of HCC unrelated to hepatitis virus infection, the contribution of metabolic factors among the overall etiology, if any, will soon likely increase. The small number of cases prevented us from restricting analysis to HBV-positive subjects, and is a limitation of this study. Whether the effect of metabolic factors on HCC differs between those positive and negative for hepatitis virus infection, and between those positive for HCV and for HBV, is not conclusive for lack of consistency between studies.

The major strength of this study is its prospective design, in which information was collected before the subsequent diagnosis of HCC, thereby avoiding the exposure recall bias inherent with case–control studies. Other strengths include: study subjects were selected from the general population; the proportion of loss to follow-up (0.3%) was negligible; the quality of our cancer registry system was satisfactory over the study period; and potential confounding factors could be adjusted to minimize their influence on risk values, in spite of the possible influence of residual confounding.

Against this, several obvious limitations can be identified. First, waist circumference was not available to assess exposure. However, given previous studies that a BMI of 25.0 kg/m^2 was equal to 100 cm^2 of visceral fat area as central obesity [32], misclassification by the use of BMI instead of waist circumference, if any, might be small. Likewise, we used non-fasting data, in particular non-fasting triglycerides $\geq$1.69 mmol/l (150 mg/dl), as a component of the metabolic factors, although justification for the use of the same cut-off point as for fasting status is presently under debate. In this study, nevertheless, analyses limited to fasting subjects yielded closely similar results.

Second, evaluation by single measurement of components of metabolic factors at baseline might have produced misclassification, even though this would likely have been non-differential and might lead to an underestimation of results. Further, the subjects of this study were restricted to 26% of the total study subjects with complete questionnaire responses and health checkup data. More women than men tend to participate in health checkup surveys provided by local governments. Further, participants often differ from nonparticipants in socioeconomic status and have a more favorable lifestyle profile, such as lower smoking rates, greater participation in physical exercise, and higher intake of green vegetables and fruits, particularly women [45, 46]. Differences in these factors may have influenced the association between metabolic factors and HCC. In addition, the incidence of HCC in this study population during the follow-up period was 45.7 per 100,000 person-years versus 67.5 in the whole JPHC Study, suggesting that subjects who were already under care for hepatitis virus infection or any of the components of metabolic factors may have been less willing to attend a health checkup. Together, these considerations mandate the need for caution in interpreting or generalizing these results.

Allowing for these methodological issues, metabolic factors in the aggregate may have been associated with an increased risk of HCC in the study population. The effects of overweight and high glucose state appear to have been the main contributors to this association, even under the condition of HCV infection. Our results imply the need to include obesity and diabetes as a crucial target in preventing progression to HCC, even among those already infected with HCV.

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Appendix

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RESEARCH COMMUNICATION

Site-specific Cancer Risk Due to Diabetes Mellitus History: Evidence from the Japan Collaborative Cohort (JACC) Study

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Abstract

The study examined the association of diabetes mellitus (DM) history with total and common site-specific cancers using a large cohort of 23,378 men and 33,503 women, extracted from 127,477 healthy participants of the JACC Study who were aged 40-79 years and living in 24 municipalities in Japan. At enrolment during 1988-90, each subject completed a self-administered questionnaire including items for age, sex, body mass index (BMI), smoking, drinking, past history of DM and cancer. Adjusting for age, BMI, smoking, and drinking in the Cox's proportional hazard model, incidence rate ratios (IRR) with 95% confidence intervals (95%CIs) were estimated for both sexes. During the follow-up period, total cancers and site-specific cancers were identified. A history of DM was reported by 7.5% of men and 4.6% of women. DM significantly increased the risk of liver cancer for both men (IRR=2.30; 95%CI=1.47-3.59) and women (IRR=2.70; 95%CI=1.20-6.05). Significant increased and reduced risk due to DM for men were also found for non-Hodgkin lymphoma (IRR=2.77; 95%CI=1.04-7.38) and stomach cancer (IRR=0.67; 95%CI=0.46-0.99) respectively. For females, a reduced risk of stomach cancer due to DM (IRR=0.49; 95%CI=0.23-1.04) was also revealed. Since a history of DM here demonstrated significant associations with some site-specific cancers, their relationships should be studied further in Japan for validation.

Key Words: Diabetes mellitus - liver cancer - stomach cancer - cohort study - Japan

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Introduction

Worldwide the disease profiles have shifted remarkably from a communicable to a chronic and non-communicable disease (International Union for Health Promotion and Education, 2000). Diabetes mellitus (DM) - a non-communicable disease - is a serious and costly ailment that is becoming increasingly common in many countries (Jee et al, 2005). Islam et al (3) reported an increasing trend of DM in Japan, ranging from 1.8-6.9% during 1964-79 to 9.6-11.9% during 1990-92 for people aged 40 and over. This trend may be attributable both to the demographic changes due to greater longevity and to the increasing obesity associated with sedentary life styles of the middle aged and elderly (Neil, 2003). Like DM, cancer is also increasing and has been the leading cause death in Japan since 1981, accounting for 31% of the total that occurred in 2000 (Health and Welfare Statistics Association, 2002).

Both cohort (Smith et al, 1992; Wideroff et al, 1997; Koskinen et al, 1998; Batty et al, 2004; Coughlin et al, 2004; Jee et al, 2005) and case-control studies (La Vecchia et al, 1994) have indicated elevated risk among diabetic subjects for several cancers, notably in the breast, colon, kidney, liver, and pancreas (Mori et al, 2000). Unfortunately the role of DM still remains inconclusive (Fujino et al, 2001; Jee et al, 2005) because some cohort studies (Koskinen et al, 1998; Fujino et al, 2001; Jee et al, 2005) reported DM as a risk factor for total cancer whereas others (Smith et al, 1992; Saydah et al, 2003; Batty et al, 2004; Khan et al, 2006) failed to provide evidence. Particularly the DM role among Japanese is inconsistent as two Japanese cohort studies (Fujino et al, 2001, Khan et al, 2006) provided different results. Moreover, to our knowledge no big study, in terms of study subjects and areas, reported the risk of total and site-specific cancer in Japan in relation to DM history by sex. Furthermore, the findings of many studies have been

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limited by small sample sizes (Fujino et al, 2001). Considering this background, the present study was conducted to examine associations of a history of DM with total as well as common site-specific cancers using nation-wide data from the Japan Collaborative Cohort (JACC) Study.

Materials and Methods

Study Subjects

Details of the study methods adopted in the baseline and follow-up surveys are explained elsewhere (Ohno et al, 2001; Kojima et al, 2004). Briefly, the JACC Study for Evaluation of Cancer Risk (sponsored by the Ministry of Education, Culture, Sports, Science and Technology of Japan) is a large nation-wide multicenter prospective cohort study in which 127,477 apparently healthy inhabitants from 45 municipal areas (6 cities, 34 towns and 5 villages) located in 7 districts (out of 8) of Japan who responded the study questionnaire between 1988 and 1990 are enroled . Enrolment was based on participants' general health check-ups periodically provided by the municipalities. Informed consent for participation was obtained using two strategies, either by signing the cover page of the questionnaire (at the individual level which covered the majority of the participants) or by explaining the aim of the study and confidentiality of the data (at the group level) to the community leader (Kojima et al, 2004). For analytical purposes, this study only included the subjects aged 40-79 years at baseline survey and who were living in the incidence survey areas. This provided a total of 65,184 subjects, of which 8,303 were again excluded for the following reasons. The year of cancer incidence was found to be registered before baseline survey for 314 subjects. Subjects with past medical history of cancer were 815 and subjects with missing information on DM were 7,174 at baseline survey. Thus we had a total of 56,881 subjects (23,378 men and 33,503 women) for analysis.

History of diabetes mellitus and other variables

At the time of enrolment, the subjects completed a self-administered questionnaire that covered: demographic characteristics such as age, sex, level of education, marital status, body mass index (BMI, kg/m^2), place of residence, and occupation; lifestyle related factors such as smoking, drinking, physical activity, dietary habits, sleeping pattern, and stress; past medical history of several diseases such as history of diabetes mellitus (DM), stroke, hypertension, tuberculosis, injury, and cancer. However, the present study utilized only some of the selected variables (categories are given in parenthesis): namely age (40-49, 50-59, 60-69, 70-79), gender (male, female), BMI (<18.5, 18.5-25.0, ≥25.0), smoking (current smoker, ex-smoker, non-smoker), drinking (current drinker, ex-drinker, non-drinker), past medical history of DM (yes, no).

Determination of cancer death and incidence during the follow-up period

Follow-up surveys were conducted annually (until the end of 1999) in all 45 areas to determine the vital status of the subjects using resident registration records available in the respective municipalities. For deceased subjects, cause of death was identified from the death certificate using International Classification of Disease version 10 (ICD-10). For instance, codes of ICD-10 were C16.0 to C16.9 for stomach cancer, C18.0 to C18.9 for colon cancer, C22.0 to C22.9 for liver cancer, C25.0 to C25.9 for pancreatic cancer, C34.0 to C34.9 for lung cancer, C61.0 to C61.9 for prostate cancer, and C64.0 to C64.9 for kidney cancer. However, the incidence of cancer was ascertained only in 24 municipal areas (out of 45), where cancer registries were available. The areas with cancer registries were termed as the areas of survey for the incidence (ASI). Population-based and hospital-based cancer registries were available in 20 and 4 ASIs respectively. The end of follow-up period for cancer incidence survey was December 31, 1997 in 23 ASIs whereas it was December 31, 1994 in the remaining ASI because of accidental interruption in the survey (Kojima et al, 2004; Mori et al, 2005). ICD-10 also used to determine the cancer incidence. For the present analysis, the subjects who developed any cancer or who died of any cancer during the follow-up period in 24 ASIs (until 1994 in one ASI and after 1997 in 23 ASIs) were termed as the incident cases of total cancer and any subject alive throughout the follow-up period or who moved out the study areas or was lost to follow-up were considered as censored.

Statistical analysis

The data were handled with Statistical Analysis System (SAS) version 9.1. All the analyses were carried out separately for men and women. The outcome variables of interest were total cancer as well as common site-specific cancers for which at least 12 incident cases were available. We used the Cox proportional hazard model (PHREG procedure) (Der and Everitt, 2001) to estimate the incidence risk ratio (IRR) including 95% confidence intervals (CIs) by the past medical history of DM. Age, BMI, smoking, and drinking (as categorized above) were inserted into the Cox model as adjusting factors. All the analyses were repeated for site-specific cancer after excluding the first 2 years of follow-up.

Results

Table 1 presents the distribution of subjects, person-years of follow-up, unadjusted rate of total cancer incidence by 100,000 person-years, including the estimated total cancer IRR by some selected variables. History of DM, current smoker, and current drinker were found to be more common among men than women. For cancer incidence of men, higher rate was found in the groups of older age, lower BMI, current-smoker, ex-drinker, and subjects with history of DM. For women, older age group, higher BMI, ex-smoker, ex-drinker, and subjects with DM revealed higher rate of total cancer incidence. The multivariate Cox model indicated that

Table 1. Distribution of Subjects, Person-years (P-Ys), Cancer Incidence, Incidence Risk Ratio (IRR), and 95% Confidence Iinterval (95%CI) by Some Selected Variables, JACC Study, 1988-1997.

Variables	Subjects		Person-years	Incidence		Cox model		
	n	%		cases	/10^{5}P-Ys	IRR	95%CI	P-Value
Men (total):	23378	100.0	189567.2	1948	1027.6	-	-	-
Age:								
40-50 (RC)	6179	26.4	52410.1	169	322.5	1.00	-	-
50-60	7096	30.4	58647.0	441	752.0	2.50	2.08 - 3.03	<0.0001
60-70	6755	28.9	53151.3	802	1508.9	4.75	3.97 - 5.67	<0.0001
70-80	3348	14.3	25358.8	536	2113.7	6.83	5.64 - 8.26	<0.0001
BMI (kg/m^2):								
<18.5	1184	5.1	9300.5	134	1440.8	1.08	0.89 - 1.30	0.4283
18.5-25.0 (RC)	16969	72.6	137554.9	1422	1033.8	1.00	-	-
≥25.0	4124	17.6	33778.8	288	852.6	0.93	0.81 - 1.06	0.2931
History of DM:								
No (RC)	21625	92.5	176754.5	1795	1015.5	1.00	-	-
Yes	1753	7.5	12812.8	153	1194.1	0.98	0.81 - 1.17	0.7906
Smoking:								
Non-smoker (RC)	4693	14.4	38739.1	281	725.4	1.00	-	-
Current smoker	11845	50.7	96607.3	1073	1110.7	1.54	1.34 - 1.77	<0.0001
Ex-smoker	5864	25.1	46151.6	488	1057.4	1.19	1.02 - 1.39	0.0284
Drinking:								
Non-drinker (RC)	4188	17.9	34037.4	343	1007.7	1.00	-	-
Current drinker	16824	72.0	136487.7	1297	950.3	1.08	0.95 - 1.22	0.2456
Ex-drinker	1341	5.7	10513.8	180	1712.0	1.51	1.25 - 1.83	<0.0001
Women (total):	33503	100.0	268041.2	1360	507.4	-	-	-
Age:								
40-50 (RC)	8434	25.2	69857.7	180	257.7	1.00	-	-
50-60	10566	31.5	85920.7	349	406.2	1.54	1.27-1.86	<0.0001
60-70	9841	29.4	76068.3	472	620.5	2.44	2.03-2.93	<0.0001
70-80	4662	13.9	36194.4	359	991.9	3.59	2.95-4.38	<0.0001
BMI (kg/m^2):								
<18.5	1955	5.8	15478.7	80	516.8	0.94	0.74-1.20	0.6373
18.5-25.0 (RC)	22771	68.0	181865.5	837	460.2	1.00	-	-
≥25.0	7121	21.3	57483.8	322	560.2	1.17	1.02-1.34	0.0242
History of DM:								
No (RC)	31949	95.4	256864.9	1298	505.3	1.00	-	-
Yes	1554	4.6	11176.3	62	554.7	0.83	0.61-1.12	0.2104
Smoking:								
Non-smoker (RC)	29041	86.7	234667.7	1190	507.1	1.00	-	-
Current smoker	1546	4.6	12405.1	67	540.1	1.20	0.92-1.57	0.1721
Ex-smoker	434	1.3	3312.2	25	754.8	1.37	0.88-2.12	0.1603
Drinking:								
Non-drinker (RC)	24014	71.7	194562.7	1028	528.4	1.00	-	-
Current drinker	7316	21.8	56735.5	245	431.8	0.95	0.82-1.10	0.4851
Ex-drinker	511	1.5	3949.7	24	607.6	0.91	0.55-1.51	0.7219

IRR was significantly (P<0.0001) higher for all older age groups for both men and women as compared to lowest age category (reference category: RC). Higher BMI revealed significantly higher cancer IRR (P=0.0242) for women but not for men. Smoking showed significantly increased cancer IRR only for male current smoker (P<0.0001) and male ex-smoker (P=0.0284). Although male ex-drinker demonstrated significantly higher (P<0.0001) cancer IRR, female ex-drinker failed to exhibit such evidence. Finally history of DM did not show any meaningful association with total cancer for both men (P=0.7906) and women (P=0.2104).

Table 2 demonstrates incidence cases of male site-specific cancers including estimated IRR and 95%CI by history of DM under two scenarios represented by Model I (all subjects irrespective of the follow-up period) and Model II (subjects with ≥2 person-years of follow-up). Under Model I, a positive history of DM demonstrated significantly higher IRRs for liver cancer (IRR=2.30; 95%CI=1.47-3.59), and non-Hodgkin lymphoma (NHL) (IRR=2.77; 95%CI=1.04-7.38). Non-significantly elevated IRRs were found for pancreatic cancer (IRR=1.97; 95%CI=0.93-4.19, P=0.0779), and multiple myeloma (RR=3.55; 95%CI=0.94-13.39, P=0.0611). On the contrary, history of DM was found to be significantly protective for stomach cancer (IRR=0.67; 95%CI=0.46-0.99, P=0.0453). Under Model II, positive history of DM showed significantly higher risk (IRR=2.09;

Table 2. Adjusted Incidence Rate Ratios (IRRs) for Site-specific Cancers and 95% Confidence Intervals (95%CIs) by History of Diabetes Mellitus (DM) among Men, JACC Study, 1988-1997

Site-specific cancer	Before exclusion (cases=1,656)				Follow-up <2 years excluded (cases=1449)			
	Cases	IRR	95%CI	P-value	Cases	IRR	95%CI	P-value
Stomach	496	0.67	0.46 - 0.99	0.0453	416	0.72	0.40 - 1.09	0.1222
Colon	165	1.33	0.79 - 2.23	0.2850	143	1.39	0.80 - 2.43	0.2410
Rectum	131	0.95	0.48 - 1.88	0.8864	110	1.21	0.61 - 2.40	0.5897
Liver	136	2.30	1.47 - 3.59	0.0002	115	2.09	1.26 - 3.47	0.0045
Gallbladder	12	1.08	0.14 - 8.43	0.9405	11	-		
Biliary tract	43	0.57	0.14 - 2.36	0.4371	40	0.30	0.04 - 2.22	0.2403
Pancreas	58	1.97	0.93 - 4.19	0.0779	54	1.57	0.67 - 3.68	0.3053
Lung	269	0.71	0.42 - 1.19	0.1939	240	0.71	0.41 - 1.25	0.2331
Prostate	98	0.98	0.47 - 2.03	0.9521	94	1.04	0.50 - 2.16	0.9173
Kidney	25	1.10	0.26 - 4.72	0.8951	22	1.32	0.31 - 5.69	0.7111
Bladder	60	1.03	0.41 - 2.60	0.9461	52	1.25	0.49 - 3.16	0.6427
Non-Hodgkin lymphoma	28	2.77	1.04 - 7.38	0.0418	27	2.21	0.75 - 6.46	0.1488
Multiple myeloma	12	3.55	0.94 -13.39	0.0611	12	3.55	0.94 -13.39	0.0611

Note: adjusted for categorical variables of age, BMI, smoking, and drinking shown in Table 1.
Esophagus was not shown because Cox model failed to calculate its IRR.

Table 3. Adjusted Incidence Rate Ratios (IRRs) for Site-specific Cancers and 95% Confidence Intervals (95%CIs) by History of Diabetes Mellitus (DM) among Women, JACC Study, 1988-1997

Site-specific cancer	Before exclusion (cases=1,139)				Follow-up <2 years excluded (cases=980)			
	Cases	IRR	95%CI	P-value	Cases	IRR	95%CI	P-value
Stomach	265	0.49	0.23 - 1.04	0.0639	215	0.26	0.08 - 0.82	0.0211
Colon	139	1.00	0.46 - 2.15	0.9983	121	1.02	0.44 - 2.33	0.9706
Rectum	44	2.54	0.89 - 7.25	0.0809	42	2.70	0.94 - 7.71	0.0645
Liver	55	2.70	1.20 - 6.05	0.0161	48	2.55	1.07 - 6.10	0.0352
Gallbladder	32	1.14	0.27 - 4.83	0.8634	27	1.30	0.30 - 5.57	0.7285
Pancreas	76	1.42	0.61 - 3.29	0.4182	69	1.63	0.70 - 3.80	0.2616
Lung	87	0.21	0.03 - 1.47	0.1152	72	0.25	0.03 - 1.77	0.1637
Breast	120	1.27	0.51 - 3.14	0.6077	101	1.55	0.62 - 3.85	0.3457
Cervix of uterus	26	0.99	0.13 - 7.38	0.9883	22	-	-	-
Ovary	30	1.82	0.42 - 7.87	0.4212	29	1.86	0.43 - 8.05	0.4058
Kidney	12	2.36	0.30 -18.53	0.4159	11	2.79	0.35 -22.16	0.3324
Non-Hodgkin lymphoma	19	1.34	0.18 -10.14	0.7799	17	1.40	0.18 -10.66	0.1028

Note: adjusted for categorical variables of age, BMI, smoking, and drinking shown in Table 1.
Esophagus, biliary tract, bladder, and multiple myeloma were not shown because Cox model failed to calculate IRR for them.

95%CI=1.26-3.47) only for liver cancer. Although stomach cancer and NHL lost their significance level under Model II, their direction remained the same.

Table 3 similarly reveals the incidence cases of female site-specific cancers including estimated IRR and 95%CI by history of DM under the same scenarios of Model I and Model II (given above). Model I indicated that positive history of DM was significantly positively associated only with liver cancer (IRR=2.70; 95%CI=1.20-6.05). Other remarkable findings may include the positive association of history of DM with rectum cancer (IRR=2.54; 95%CI=0.89-7.25, P=0.0809) and negative association with stomach cancer (IRR=0.49; 95%CI=0.23-1.04, P=0.0639). Under Model II, DM history significantly increased the IRR for liver cancer (IRR=2.55; 95%CI=1.07-6.10) and significantly decreased the IRR for stomach cancer (IRR=0.26; 95%CI=0.08-0.82). The associations of DM history with rectum cancer (IRR=2.70; 0.94-7.71, P=0.0645) and NHL (IRR=1.40; 95%CI=0.18-10.66, P=0.1028) became stronger.

Discussion

Present study examined the history of DM as a risk factor of cancer using a large data set for the first time to our knowledge, which might be important as both DM and cancer are increasing in Japan. Our study clearly demonstrated significantly increased risk of liver cancer due to DM, which was consistently supported by many studies (Adami et al, 1991; La Vecchia et al, 1994; Adami et al, 1996; La Vecchia et al, 1997; Wideroff et al, 1997; Lagiou et al, 2000; Mori et al, 2000; Batty et al, 2004; Coughlin et al, 2004; El-Serag et al, 2004) including Japan (Fujino et al, 2001; Shibata et al, 2003). Several mechanisms including the mechanism of hyperinsulinemia have been proposed in favor of increasing risk of liver cancer. Cerhan et al (1997) suggested that DM is preceded by a long period of insulin resistance syndromes, i.e., a compensatory hyperinsulinemia, abnormal carbohydrate and lipid metabolism, and other metabolic alterations. Insulin stimulates cell growth, either

directly through the insulin receptor, or through its ability to cross-react with insulin like growth factors I (IGF-I) receptor, and it is generally held that growth factors are likely to play an important role in carcinogenesis. According to El-Serag et al (2004), DM has preceded the development of chronic liver disease and the chronic liver disease associated with DM is usually insidious and asymptotic and goes undetected until a severe manifestation such as hepatocellular carcinoma (HCC) occurs. Kaido et al (2002) found that liver dysfunction is significantly higher for the hyperglycemic group than normal group. Fujino et al (2001) mentioned that the liver of the diabetic patients may undergo fatty changes (steatosis), with the potential for necrosis (steatohepatitis) and fibrotic progression of cirrhosis, perhaps resulting from the cellular accumulation of toxic free fatty acids in insulin-deficient cells. Since diabetic patients have higher frequency of hepatitis C than general population, it might contribute to both prolonged insulin resistance (hence to diabetes) and liver cancer (Balkau et al, 2001). It should be noted that more than 80% of HCC cases are found to be associated with hepatitis C virus (HCV) in Japan (Yoshizawa, 2002). Hyperinsulinemic individuals are more vulnerable to hepatic carcinogens because they have an impaired adenosine triphosphatase homeostasis in the liver (Cortez-Pinto et al, 1999). Moreover, the presence of DM worsens the prognosis of patients with HCC by means of a rapid decline in remnant liver function caused by repeated treatment (Toyoda et al, 2001) may be another reason.

We analyzed the association of DM with total cancer including (Table 1) and excluding (not shown) liver cancer for both men and women to understand their changes. The IRRs were less than unity under both analyses and found to be insignificantly associated. However, the association of DM was stronger for total cancer excluding liver cancer (men: IRR=0.86; P=0.1472; women: IRR=0.73; P=0.0614) than including it (IRR=0.98; P=0.7906; women: IRR=0.83; P=0.2104). Some previous cohort studies (Smith et al, 1992; Saydah et al, 2003; Batty et al, 2004; Khan et al, 2006) similarly reported insignificant association between DM and total cancer. However, few cohort studies (Koskinen et al, 1998; Fujino et al, 2001; Jee et al, 2005) demonstrated DM as a significant risk factor for total cancer and emphasized on the above-mentioned mechanism of hyperinsulinemia. Based on the present findings, it may be noted that the generalizability of the insulin based mechanism for total cancer may be misleading in Japan.

DM showed significant lower risk for stomach cancer for both men and women even after adjusting four important factors. This finding is opposite to the findings of Wideroff et al (1997) and Jee et al (2005), which provided significantly increased risk for stomach cancer for both sexes. Higher but insignificant risk ratio was reported by other cohort studies (Koskinen et al, 1998; Smith et al, 1992; Batty et al, 2004). Only one cohort study reported the RR less than unity for stomach cancer due to DM for men but not for women (Coughlin et al, 2004). Because of such inconsistencies, perhaps the explanation of the mechanism between stomach cancer and DM is not straightforward. However, it should be noted that recently stomach cancer incidence is gradually decreasing in Japan.

Our data revealed positive association between NHL and history of DM among men. However, the causal association between them may be uncertain. Because several studies reported significant positive association between NHL and DM (Natazuka et al, 1994; Cerhan et al, 1997; Hjalgrim et al, 1997) and several studies reported decreased risk from NHL among the people with DM (La Vecchia et al, 1994; Zahm et al, 1995). Only one study (Adami et al, 1991) reported no association between DM and NHL. Coughlin et al (2004) reported almost significantly higher risk (RR=1.21; 95%CI= 0.99-1.48) from NHL due to DM among men but not in women (RR=0.93; 95%CI=0.71-1.21). Possible mechanisms between DM and NHL have been explained elsewhere (Natazuka et al, 1994; Cerhan et al, 1997). Briefly, DM impairs the immune response to infectious agents which might increase the risk of NHL.

Although history of DM was insignificantly related with pancreatic cancer by our study, several studies reported DM as a significant risk factor for it (Adami et al, 1991; La Vecchia et al, 1994; Wideroff et al, 1997; Silverman et al, 1999; Fisher, 2001; Batty et al, 2004; Coughlin et al, 2004; Jee et al, 2005). However the direction was same among all studies. As a causal mechanism, Fisher (2001) suggested the possibility of destruction of the endocrine pancreas by tumor invasion. The tumor obstructs the pancreatic duct and causes distal pancreatitis and subsequent dysfunction of the endocrine pancreas. DM also showed insignificant but elevated risk (IRR=2.54) for rectum cancer for women. Almost all studies (La Vecchia et al, 1994; Wideroff et al, 1997; Hu et al, 1999; Coughlin et al, 2004; Limburg et al, 2005) reported insignificant association except one (La Vecchia et al, 1997a) where OR=1.5 and 95%CI=1.1-2.2. Therefore we recommended further studies to evaluate whether the increased risk of rectum cancer due to DM is confounding effect or not.

Elevated risk of multiple myeloma (IRR=3.55, P=0.0611) in men due to DM history may indicate the importance of further research in Japan as both DM (Islam et al, 1999) and multiple myeloma (Sonoda et al, 2005) are increasing. Based on a cohort study, Coughlin et al (2004) also reported almost significantly higher risk (RR=1.27; 95%CI=0.98-1.66) of multiple myeloma in men. However, these findings contradicted with the finding of another cohort study (Wideroff et al, 1997) where reported standardized incidence ratio was unity. Two case-control studies (La Vecchia et al, 1994; Sonoda et al, 2005) also revealed odd ratios of less than unity among diabetic subjects. As the associations between DM and multiple myeloma are inconsistent, further research may be necessary to validate the results.

History of DM showed some protective effect (although insignificant) on lung cancer for both men and women. Similarly a negative association was reported by some cohort studies (Smith et al, 1992; Wideroff et al, 1997; Koskinen

et al, 1998; Batty et al, 2004; Hall et al, 2005). This particular findings differed from other study (Coughlin et al, 2004) that showed the RR>1 for both men and women. Adjusting age, age squared, smoking and drinking, Jee et al (2005) also found slightly higher but insignificant RR (>1) for men and significantly higher RR for women. Unfortunately none of these studies (Smith et al, 1992; Koskinen et al, 1998; Coughlin et al, 2004; Jee et al, 2005) explained the possible mechanism of increased or decreased lung cancer with respect to DM. Although two cohort studies (Koskinen et al, 1998; Batty et al, 2004), that reported significantly lower risk, explained that generally lower prevalence of smoking among diabetics might be related to the protective effect, but for the present study it is unclear as we adjusted smoking into the Cox model. Hall et al (2005) suggested that shorter life expectancy in diabetes results less opportunity for lung cancer.

The main advantage of the study is the large number of subjects covering almost whole nation. However, this study may have some criticisms. One criticism may be related to the classification of subjects (diabetic versus non-diabetic) based on their report including a lot of missing information. El-Serag et al (2004) reported that DM is frequently under diagnosed and under reported and hence subjects in the non-diabetic group may have had DM. We adjusted only four factors such as age, BMI, smoking, and drinking in the Cox model, which may be not sufficient for studying the total as well as site-specific cancer. For example, we could not adjust the influence of HCV due to the lack of such information at the baseline survey of JACC study, although HCV is a major cause of HCC (>80% of HCC is caused by it) in Japan (Yoshizawa et al, 2002).

Finally based on the study findings, it can be concluded that DM might be a risk factor for liver cancer for both men and women. However, further prospective studies are needed to confirm other findings as both total cancer (except stomach cancer) and DM are simultaneously increasing in Japan.

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The present members of the JACC Study and their affiliations are as follows: Dr. Akiko Tamakoshi (present chairman of the study group), Nagoya University Graduate School of Medicine; Dr. Mitsuru Mori, Sapporo Medical University School of Medicine; Dr. Yutaka Motohashi, Akita University School of Medicine; Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine; Dr. Yosikazu Nakamura, Jichi Medical School; Dr. Hiroyasu Iso, Institute of Community Medicine, University of Tsukuba; Dr. Haruo Mikami, Chiba Cancer Center; Dr. Yutaka Inaba, Juntendo University School of Medicine; Dr. Yoshiharu Hoshiyama, University of Human Arts and Sciences Graduate School; Dr. Hiroshi Suzuki, Niigata University Graduate School of Medical and Dental Sciences; Dr. Hiroyuki Shimizu, Gifu University School of Medicine; Dr. Hideaki Toyoshima, Nagoya University Graduate School of Medicine; Dr. Shinkan Tokudome, Nagoya City University Graduate School of Medicine; Dr. Yoshinori Ito, Fujita Health University School of Health Sciences; Dr. Shuji Hashimoto, Fujita Health University School of Medicine; Dr. Shogo Kikuchi, Aichi Medical University School of Medicine; Dr. Kenji Wakai, Aichi Cancer Center Research Institute; Dr. Akio Koizumi, Graduate School of Medicine, Kyoto University; Dr. Takashi Kawamura, Kyoto University Center for Student Health; Dr. Yoshiyuki Watanabe and Dr. Tsuneharu Miki, Kyoto Prefectural University of Medicine; Dr. Chigusa Date, Mukogawa Women's University; Dr. Kiyomi Sakata, Wakayama Medical University; Dr. Takayuki Nose, Tottori University Faculty of Medicine; Dr. Norihiko Hayakawa, Research Institute of Radiation Biology and Medicine, Hiroshima University; Dr. Takesumi Yoshimura, University of Occupational and Environmental Health; Dr. Akira Shibata, Kurume University School of Medicine; Dr. Naoyuki Okamoto, Kanagawa Cancer Center; Dr. Hideo Shio, Moriyama Municipal Hospital/Shiga Medical Center; Dr. Tomoyuki Kitagawa, Cancer Institute of the Japanese Foundation for Cancer Research; Dr. Toshio Kuroki, Gifu University; and Dr. Kazuo Tajima, Aichi Cancer Research Institute.

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Short Communication

Liver cancer risk, coffee, and hepatitis C virus infection: a nested case–control study in Japan

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We examined hepatocellular carcinoma mortality in relation to coffee consumption and anti-hepatitis C virus (HCV) antibody seropositivity in a nested case–control study involving 96 cases. The multivariate-adjusted odds ratios (95% confidence interval) for daily coffee drinkers vs non-drinkers were 0.49 (0.25–0.96), 0.31 (0.11–0.85), and 0.75 (0.29–1.92) in all cases, in HCV-positive and in HCV-negative individuals, respectively.

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The inverse associations between coffee consumption and the risk of hepatocellular carcinoma (HCC) have recently been reported not only from case–control studies (Gallus *et al*, 2002; Gelatti *et al*, 2005; Ohfuji *et al*, 2006; Montella *et al*, 2007; Tanaka *et al*, 2007) but also from Japanese cohort studies (Inoue *et al*, 2005; Kurozawa *et al*, 2005; Shimazu *et al*, 2005). Cohort studies are superior to case–control studies in avoiding recall and selection bias (Ohfuji *et al*, 2006). Previous prospective studies (Inoue *et al*, 2005; Kurozawa *et al*, 2005; Shimazu *et al*, 2005), however, did not consider the infection status of hepatitis C virus (HCV) at baseline. As HCV is the major cause of HCC in Japan and certain other countries (Heathcote, 2004), it would be important if protective factors against HCC could be found among the HCV-positive population. We therefore examined the relation of coffee use to risk of death from HCC by HCV infection status in a case–control study nested in a large cohort study in Japan.

MATERIALS AND METHODS

We carried out a nested case–control study as a part of the Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by the Ministry of Education, Culture, Sports, Science and Technology of Japan (Mobusho), details of which are described elsewhere (Tamakoshi *et al*, 2005). It involved 110 792 individuals, aged 40–79 years at baseline, from 45 areas throughout Japan. A self-administered questionnaire on lifestyle and medical factors was distributed in 1988–1990 covering habitual coffee consumption, with possible responses including 'scarcely any', '1–2 cups per month', '1–2 cups per week', '3–4 cups per week', and 'almost every day'. Those who answered 'almost every day' were asked to report the number of cups consumed per day. The questionnaire was validated using four 3-day dietary records as a reference; the Spearman correlation coefficient was 0.79 (Iso *et al*, 2006).

In addition, those participants who underwent health-screening checks sponsored by municipalities were asked to donate blood samples at baseline and eventually, 39 242 subjects in 37 study areas did so (Tamakoshi *et al*, 2005), these being stored at −80°C until analysed. Informed consent was obtained individually from subjects, except in certain areas in which it was provided at the group level after details had been explained to community leaders. The Ethics Committee of Kurume University School of Medicine approved this study.

We used population registries in the municipalities to determine the vital and residential status of the subjects. Causes of death were confirmed by review of death certificates with permission from the Ministry of Internal Affairs and Communications. Cases eligible for the present study consisted of those who died of HCC, ICD-10 coded C22.0.

During follow-up through the end of 1999, 106 eligible cases were identified among the participants with serum samples, from which two were excluded with insufficient samples and eight without information on coffee consumption. Of the remaining 96 cases, 60 (62.5%) were positive for HCV Ab. As potential controls, sera of 11 513 subjects from the same geographical areas as the cases were also screened for HCV Ab. After excluding those with missing data on coffee drinking, we found 912 HCV-Ab-positive subjects (8.2%) and 10 175 HCV-Ab-negative ones. From these, we chose as many controls per case as possible, matching for age (same 5-year strata), sex, and HCV-Ab seropositivity, selecting 420

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HCV-Ab-positive controls (seven controls per case) and 3024 HCV-Ab-negative ones (84 controls per case).

Statistical analysis

Study participants were categorised into three groups by coffee consumption, that is, $\geqslant 1$ cup day^{-1}, <1 cup day^{-1} ('1–2 cups month^{-1}', '1–2 cups week^{-1}', or '3–4 cups week^{-1}'), and non-drinkers. Daily drinkers could not be further subdivided because of their small numbers. Odds ratios (OR) and the 95% confidence intervals (CI) by HCV-Ab positivity were estimated considering the matching using conditional logistic models (Breslow and Day, 1980). Multivariate-adjusted OR were also computed after adjustment for area, smoking and drinking habits, and history of diabetes mellitus and liver diseases. For alcohol drinking, subjects were categorised into never drinkers, former drinkers, or current drinkers who consumed <2 or $\geqslant 2$ Japanese drinks per day (one Japanese drink is equivalent to 23 g of ethanol) in this analysis. The linear trend in HCC risk was tested by treating the coffee consumption category as an ordinal variable. The heterogeneity in the association of coffee drinking by HCV status was statistically tested by incorporating a multiplicative interaction term between HCV status and the coffee consumption category in the model. Missing values for each covariate were treated as an additional category in the variable and were included in the model. All *P*-values were two-sided, and all the analyses were carried out using the Statistical Analysis System version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Cases and controls were well matched on age and sex in both the HCV-positive and -negative groups. The mean ages $\pm$ s.d. were 62.9 ± 6.6, 62.4 ± 6.2, 63.6 ± 7.5, and 63.4 ± 7.3 years in the HCV-positive cases and controls and the HCV-negative cases and controls, respectively. Women accounted for 35.0% of both the HCV-positive cases and controls, and 36.1% of the HCV-negative cases and controls. Case subjects were more likely to currently smoke than controls in the HCV-positive group (56.6 *vs* 35.8%). Former drinkers and a history of diabetes mellitus and liver diseases were much more common in cases than in controls. In the HCV-positive cases, the proportions of former drinkers and those with diabetes and liver diseases were 28.6, 15.0, and 56.7%, respectively, against 6.6, 5.0, and 20.7% in the controls. The corresponding figures were 14.3, 13.9, and 27.8% in the HCV-negative cases and 4.4, 4.5, and 4.4% in the controls.

Drinking one or more cups of coffee per day was inversely associated with HCC mortality among all subjects (Table 1: multivariate-adjusted OR (OR2), 0.49; 95% CI, 0.25–0.96) and the anti-HCV-positive group (OR2, 0.31; 95% CI, 0.11–0.85). Although daily coffee drinkers in the HCV-negative group showed OR below unity, they did not reach statistical significance. The heterogeneity in the association of coffee drinking by HCV status was also not significant in the multivariate model ($P = 0.61$).

DISCUSSION

Coffee drinking was significantly associated with a decreased risk of death from HCC in all subjects and those infected with HCV. Our results from this prospective cohort study support the findings in some (Gelatti *et al*, 2005; Ohfuji *et al*, 2006), although not all (Montella *et al*, 2007), case–control studies that suggested a protective effect of coffee among HCV-positive individuals. Some patients with hepatitis or liver cirrhosis, however, may have decreased coffee consumption at their physician's advice or due to impaired caffeine metabolism in the liver (Hasegawa *et al*, 1989). Observational studies among subjects without active hepatitis or intervention

Table 1 OR and 95% CI for HCC mortality according to coffee consumption by anti-HCV-antibody seropositivity

Coffee consumption	All subjects					Anti-HCV-positive group					Anti-HCV-negative group				
	No. of cases	No. of controls	OR1[a]	95%CI	OR2[b]	95%CI	No. of cases	No. of controls	OR1[c]	95%CI	OR2[b]	95%CI	No. of cases	No. of controls	OR1[c]	95%CI	OR2[b]	95%CI
Non-drinkers	44	1163	1.00		1.00		28	147	1.00		1.00		16	1016	1.00		1.00	
<1 cup day^{-1}	34	1266	0.72	0.45–1.15	0.77	0.45–1.32	23	153	0.79	0.44–1.42	0.91	0.41–2.04	11	1113	0.62	0.29–1.35	0.65	0.29–1.46
$\geqslant 1$ cup day^{-1}	18	1015	0.49	0.28–0.86	0.49	0.25–0.96	9	120	0.39	0.18–0.87	0.31	0.11–0.85	9	895	0.63	0.28–1.45	0.75	0.29–1.92
P-value for trend				0.012		0.038				0.022		0.031				0.24		0.45

CI, confidence intervals; OR, odds ratios. [a]Considered for age, sex, and anti-HCV-antibody seropositivity using a conditional logistic model. [b]Further adjusted for area, smoking and drinking habits, and history of diabetes mellitus and liver diseases. [c]Considered for age and sex using a conditional logistic model.

studies will further clarify the role of coffee in the possible prevention of HCV-related HCC. Further, because a nonsignificant inverse association was found between coffee consumption and HCC risk in HCV-negative individuals in the present study, investigations with more HCV-negative HCC cases are also warranted.

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Appendix A

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Risk of Recurrence in a Long-term Follow-up After Surgery in 417 Patients With Hepatitis B- or Hepatitis C-Related Hepatocellular Carcinoma

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Objective: The aim of this study is to clarify the difference of risk of recurrence after hepatic resection between patients with hepatitis B- and hepatitis C-related hepatocellular carcinoma (HCC).

Summary and Background Data: HCC is a highly recurrent carcinoma. However, consensus has not yet been reached about the relationship between hepatitis virus types and risk of recurrence in a long-term follow-up for HCC patients who underwent hepatic resection.

Patients and Methods: From the beginning of January 1990 to the end of December 1999, of 469 HCC patients who underwent curative hepatic resection, 66 (14%) patients with positive hepatitis B virus surface antigen (HBs-Ag) and negative hepatitis C virus antibody (HCV-Ab) were regarded to have B-type hepatitis (HB)-related HCC (HB-HCC) and 351 (75%) with negative HBs-Ag and positive HCV-Ab were regarded to have C-type hepatitis (HC)-related HCC (HC-HCC). A clinical follow-up was performed to assess the existence of recurrence with the median follow-up periods of 11.0 and 10.1 years for HB- and HC-HCC patients, respectively.

Results: The 3-, 5-, and 10-year disease-free survival (DFS) rates of HC-HCC (40%, 24%, and 12%, respectively) were significantly shorter than those of HB-HCC (57%, 54%, and 28%, respectively) ($P = 0.0001$). In multivariate Cox proportional hazard analysis, viral type, TNM stage, surgical margin, and Edmondson's grade were significantly associated with risk of recurrence. The risk of recurrence from the initial HCC increased to 1.93 times (95% confidence interval, 1.27–2.93) greater in HC-HCC patients than in HB-HCC patients.

Conclusion: Hepatitis viral type is an independent factor for recurrence of HCC in a long-term clinical follow-up. This finding suggests that we may need a different strategy to control postoperative recurrence by the viral types in HCC patients.

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Since the measurement of first- and second-generation hepatitis C virus antibody (HCV-Ab) has become available,[1,2] it has been elucidated that most cases of non-A and non-B type chronic hepatitis or liver cirrhosis coexisting with hepatocellular carcinoma (HCC) are C-type hepatitis (HC). The number of patients with HCC originating from HC (HC-HCC) has increased year by year, along with a decrease of patients with HCC originating from B-type hepatitis (HB) (HB-HCC), especially in Japan. According to a nationwide survey in Japan in 2003,[3] the frequency of patients with HC-HCC (72%) was much higher than that of patients with HB-HCC (17%). The frequency of HC-HCC patients in Japan is almost the same as that of patients in Italy and Spain.[4,5] However, in Asian countries around Japan, such as China, Taiwan, and Korea, where the prevalence of HCC is high, HB-HCC is still dominant.[6–8] Numerous epidemiologic and molecular-biologic studies about the association between hepatitis B virus (HBV) infection and the development of HCC have been reported.[9–11] HBV is thought to induce development of HCC through integration,[12,13] transactivation,[14] mutation of tumor suppressor genes, and so forth, in addition to carcinogenesis on the sequential process of chronic hepatitis to liver cirrhosis.[15] As the occurrence of HB-HCC is partly brought about by the direct oncogenic effect of HBV, the fibrotic change of the liver at carcinogenesis may not be so severe. On the other hand, hepatitis C virus (HCV) is an RNA virus that does not integrate to the DNA of hepatocytes, and its relationship to the oncogenic mechanism of HCC is unclear. The carcinogenic potential of HC-HCC is known to increase in proportion to the progression from chronic hepatitis to liver cirrhosis, and actually, many of HC-HCCs occur from liver cirrhosis. Different mechanisms of HCC onset for these viruses may explain the differences in clinicopathologic features. Most chronic HBV infections are vertical transmissions during delivery, whereas HCV infections are mainly blood-borne such as from transfusions after reaching adulthood. Consequently, the mean age at occurrence of HCC is lower in HB-HCC than in HC-HCC. As mentioned above, characteristic differences of some etiologic or clinical factors have been pointed out between HB- and HC-HCC patients who underwent surgery.[16,17] However, few data are available in the literature regarding the differences of recurrence between the two types of virus-originated HCC

more than 10 years after hepatic resection. Herein, to clarify the difference of risk of recurrence after hepatic resection between patients with HB- and HC-HCC, we compared the long-term postoperative disease-free survival (DFS) of HCC between the two groups.

PATIENTS AND METHODS

Subjects

From the beginning of January 1990, when HCV-Ab could be generally measured in our hospital, to the end of December 1999, 469 patients underwent curative hepatic resection and were discharged. Curative resection was defined as complete macroscopic removal of the tumor without exposure of tumor cells on the cut surface. Of these patients, 66 (14%) were seropositive for hepatitis B virus surface antigen (HBs-Ag) and seronegative for HCV-Ab, 9 (2%) were seropositive for both HBs-Ag and HCV-Ab, 351 (75%) were seronegative for HBs-Ag and seropositive for HCV-Ab, and 43(9%) were seronegative for both HBs-Ag and HCV-Ab. The HCC patients with positive HBs-Ag and negative HCV-Ab were regarded to have HB-HCC, and those with negative HBs-Ag and positive HCV-Ab were regarded to have HC-HCC. The patients with HB-HCC and HC-HCC were enrolled in this study.

Assessment and Follow-up

Hepatic resection was offered by assessment of resectability based on both tumor progression and liver functional reserve. The degree of tumor progression was judged by radiographic findings from chest x-ray, ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and hepatic angiography. Liver function status was assessed by liver biochemistry status, indocyanine green retention test for 15 minutes (ICG-R15), and Child's classification[18] as an overall estimate. No postoperative adjuvant therapies were given for all patients.

All patients were followed up for postoperative recurrence with assessment by tumor markers such as serum alpha-fetoprotein (AFP) level and serum protein induced by vitamin K absence II level, chest x-ray, and US or CT every 2 or 3 months after surgery until March 2005. At the end of March 2005, the number of patients who died of hepatic disease or other diseases without recurrence was 4 (6.1%) in HB-HCC patients and 26 (7.4%) in HC-HCC patients, respectively, and the number of patients who did not complete the follow-up about recurrence was 2 (3.0%) for HB-HCC patients and 5 (1.4%) for HC-HCC patients, respectively. When recurrence was discovered, the recurrent lesions were managed aggressively with a multimodal approach, including further surgery, transarterial chemoembolization, and percutaneous ethanol injection. The treatment method was decided by the pattern of recurrence and liver functional reserve at the time of recurrence.

Analysis

First, we compared the distributions of host factors including activity of hepatitis and liver functional reserve, tumor factors, surgical factors, and pathologic factors between the HB- and HC-HCC patients. Second, we compared the long-term survival and DFS curves after surgery between the HB- and HC-HCC patients. Moreover, to examine the differences of the DFS curves by the degree of tumor progression and liver function, HB-HCC patients and HC-HCC patients were separately stratified into these subgroups and the DFS curves of HB- and HC-HCC were compared on the same grade. TNM Stage by the Liver Cancer Study Group of Japan (LCSGJ),[19] which is concordant with TNM classification by the International Hepato-Pancreato-Biliary Association and the International Union Against Cancer (Table 1)[20] was used for the grade of tumor progression, and Child's classification was used for the grade of liver functional reserve. Finally, to examine whether viral type is associated with the risk of recurrence for HCC, we calculated hazard ratio for recurrence in univariate and multivariate analysis.

Statistics

The statistical analysis was carried out with Student t[r] test for unpaired observations and the χ^2 test for the frequency of various attributes between the groups. Survival and DFS curves were analyzed using the Kaplan-Meier method. Differences between curves were assessed according to the log-rank test. In univariate analysis, statistical comparisons between the subgroups of patients were made using the Mantel-Cox test. The Cox proportional hazards regression model was used for multivariate analysis. Differences with a P value less than 0.05 were considered significant. All P values were two-tailed. Statistical analysis was performed using a Power Macintosh G4 and Stat View 5.0 software (SAS Institute, Berkley, CA).

RESULTS

Comparison of Clinicopathologic Characters Between HB- and HC-HCC Patients

The distribution of selected characteristics by hepatitis virus among HCC patients was examined (Table 2). The percentages of older patients, patients with stronger hepatic inflammatory activity [the values of serum alanine aminotransferase (ALT)], and those with poorer liver functional reserve (the values of albumin and ICG-R15, and Child's classification) were significantly higher in the HC-HCC group than in the HB-HCC group. In tumor-related factors,

TABLE 1. Definitions of TNM Stage by the Liver Cancer Study Group of Japan

T Factor	I. Single	II. <2 cm	III. No Vascular Involvement
T1			Fulfilling 3 factors
T2			Fulfilling 2 factors
T3			Fulfilling 1 factors
T4			Fulfilling 0 factors
Stage I			T1 N0 M0
Stage II			T2 N0 M0
Stage III			T3 N0 M0
Stage IV-A			T4 N0 M0 or any T N1 M0
Stage IV-B			Any T N0-1 M1

TABLE 2. Distribution of Selected Characteristics by Viral Hepatitis Among HCC Patients Who Underwent Hepatic Resection

Characteristic	HB-HCC %	HB-HCC No.	HC-HCC %	HC-HCC No.	P(×2)
Age (yr)					
≤65	93†	61†	67†	237†	<0.0001†
>65	7†	5†	33†	114†	
Gender					
Male	74	49	76	268	0.71
Female	26	17	24	83	
ALT (IU/l)					
<80	77†	51†	50†	176†	<0.0001†
≥80	23†	15†	50†	175†	
Alb (g/dL)					
<3.5	12†	8†	25†	89†	0.01†
≥3.5	88†	58†	75†	262†	
T bil (mg/dL)					
<1.0	74	49	69	242	0.39
≥1.0	26	17	31	109	
ICG-R15 (%)*					
<20	78†	50†	58†	199†	0.003†
≥20	22†	14†	42†	147†	
Prothrombin time (%)					
≤80	20	13	22	77	0.71
>80	80	53	78	274	
Child's classification					
A	86†	57†	74†	261†	0.03†
B + C	14†	9†	26†	90†	
Preoperative TAE					
Yes	36	24	34	121	0.78
No	64	42	66	230	
AFP (ng/mL)					
≤100	44†	29†	62†	216†	0.04†
>100	56†	37†	38†	135†	
Tumor size (cm)					
≤3.0	56	37	62	219	0.36
>3.0	44	29	38	132	
No. of tumors					
1	83	55	75	263	0.16
2 or more	17	11	25	88	
TNM stage by LCSGJ					
I	23	15	25	88	
II	59	39	56	197	0.85
III + IV	18	12	19	66	
Operation time (min)					
≤180	35	23	32	112	0.63
>180	65	43	68	239	
Blood loss (mL)					
≤1000	50	33	50	177	
>1000	50	33	50	174	0.89
Surgical margin (mm)					
<10	48	32	60	209	0.12
≥10	52	34	40	142	
Transfusion					
Yes	26†	17†	48†	167†	0.0008†
No	74†	49†	52†	184†	
Resection range					
Hr0 + HrS	42†	28†	67†	234†	0.0002†
Hr1 + Hr2 + Hr3	58†	38†	33†	117†	
Edmondson's grade					
I	22	11	23	68	0.64
II	57	29	60	175	
III	22	11	16	47	
Extracapsular invasion					
Yes	60	33	52	153	0.31
No	40	22	48	139	
Satellite nodule					
Yes	33	18	27	76	
No	67	36	73	206	0.34
Venous invasion					
Yes	35	18	39	112	0.56
No	65	34	61	176	
Noncancer tissue					
Normal	6	4	4	15	0.12
Fibrosis	41	27	28	99	
Cirrhosis	53	35	68	237	

HCC, hepatocellular carcinoma; HB-HCC, hepatitis B-related hepatocellular carcinoma; HC-HCC, hepatitis C-related hepatocellular carcinoma; AFP, alpha fetoprotein; TAE, transarterial embolization; Hr0, partial resection; HrS, subsegmentectomy; Hr1, one segmentectomy; Hr2, two segmentectomy; Hr3, three segmentectomy; LCSGJ, Liver Cancer Study Group of Japan.

*Three patients were excluded because of ICG excretion abnormalities, and four were not measured. There are several deficits in microscopic factors because of necrosis by preoperative TAE.

†Factors with significant difference.

the value of serum AFP was significantly smaller in the HC-HCC group than in the HB-HCC group. However, there were no statistical differences among the factors of the tumor size, the number of tumors, or TNM stage by LCSGJ. In surgery-related factors, although no significant differences were recognized for the operation time, blood loss during operation, and surgical margin, the patients who had smaller resection range and perioperative transfusion were more likely in the HC-HCC group than in the HB-HCC group. In pathologic factors, there were no significant differences in any factors such as the grade of differentiation of the tumor (Edmondson and Steiner's classification),[21] extracapsular invasion, satellite nodules, vascular invasion, or histology of noncancerous lesions.

Comparison of Survival and DFS After Surgery Between HB- and HC-HCC Patients

The median follow-up times of HB- and HC-HCC patients were 11.0 and 10.1 years, respectively. The number of recurrent patients was 39 (59%) in HB-HCC patients and 282 (80%) in HC-HCC patients, respectively. As for the forms of first recurrence, the number and percentage of

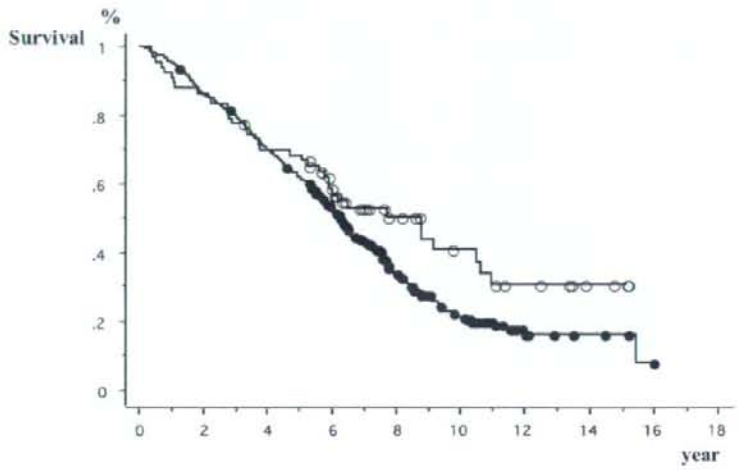

FIGURE 1. Comparison of survivals between patients with hepatitis-B-related hepatocellular carcinoma (HCC) and patients with hepatitis-C-related HCC. Open circles, hepatitis B-related HCC patients (n = 66). Closed circles, hepatitis C-related HCC patients (n = 351). Log-rank test: $P = 0.068$.

patients with intrahepatic recurrence or distant metastasis was 35 (90%) and 4 (10%) in HB-HCC patients and 273 (97%) and 9 (3%) in HC-HCC patients. The 3-, 5-, and 10-year survival rates of HB-HCC group were 78%, 69%, and 41%, respectively, and those of HC-HCC group were 80%, 62%, and 22%, respectively, and no significant difference was recognized between the survival curves of the two groups ($P = 0.068$) (Fig. 1). Until 6 years after surgery, the survival curves of both groups were almost the same. Afterward, however, they began to separate and at 10 years after surgery, the survival rate of the HC-HCC group was lower than that of the HB-HCC group. On the other hand, the 3-, 5-, and 10-year DFS rates of the HC-HCC group, 40%, 24%, and 12%, respectively, were significantly lower than those of the HB-HCC group, 57%, 54%, and 28%, respectively ($P = 0.0001$) (Fig. 2). While the DFS curve of the HB-HCC group started to slope down slowly 2 years after surgery and became almost level subsequently, the curve of the HC-HCC group kept falling until 7 years after surgery.

Comparison of DFS Curves Between the HB-HCC Group and the HC-HCC Group by TNM Stage and Child's Classification

The DFS curves between the HB-HCC group and the HC-HCC group were compared in TNM Stage by LCSGJ (Fig. 3) and Child's classification (Fig. 4), respectively. In

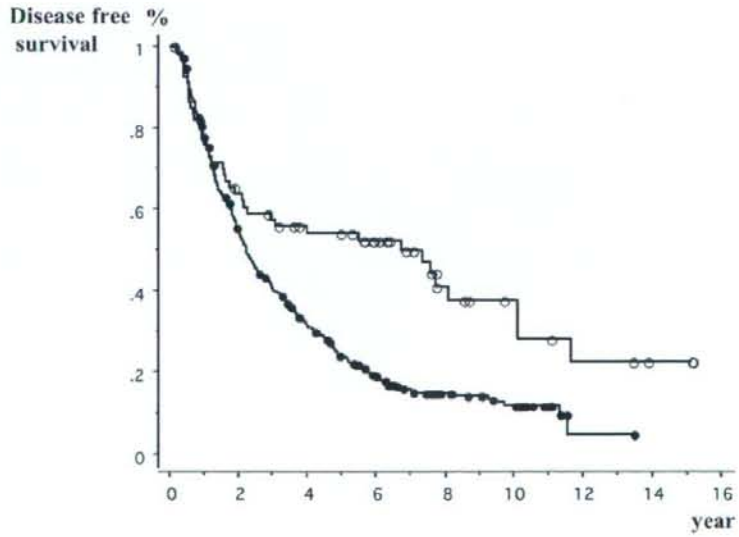

FIGURE 2. Comparison of disease-free survivals between patients with hepatitis-B-related hepatocellular carcinoma (HCC) and patients with hepatitis-C-related HCC. Open circles, hepatitis B-related HCC patients (n = 66). Closed circles, hepatitis C-related HCC patients (n = 351). Log-rank test: $P = 0.0001$.