RESEARCH COMMUNICATION

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

MMH Khan*[1], Mitsuru Mori[1], Yoshihisa Fujino[2], Akira Shibata[3], Fumio Sakauchi[1], Masakazu Washio[1], Akiko Tamakoshi[4] for the Japan Collaborative Cohort (JACC) Study Group

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

Asian Pacific J Cancer Prev, **7**, 253-259

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

*1 Department of Public Health, Sapporo Medical University School of Medicine; 2 Department of Preventive Medicine and Community Health, University of Occupational and Environmental Health, Kitakyushu; 3 Department of Public Health, Kurume University School of Medicine; 4 Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine * Corresponding author: Department of Public Health, Sapporo Medical University School of Medicine Sapporo 060-8556, Japan E-mail: khan@sapmed.ac.jp or mmhkhan70@yahoo.com*

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	/10^5P-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.

Acknowledgments

We express our sincere appreciation to Dr. Kunio Aoki, Professor Emeritus, Nagoya University School of Medicine and the former chairman of the JACC Study Group; Dr. Yoshiyuki Ohno, former chairman of the study group, Asahi Rosai hospital; and Dr. Haruo Sugano, the former Director of the Cancer Institute of the Japanese Foundation for Cancer Research, who greatly contributed to the initiation of the study.

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.

The past investigators of the JACC Study group, other than the following eight members, were listed in the reference (Ohno and Tamakoshi, 2001; affiliations are those at the time they participated in the study): Dr. Takashi Shimamoto, Institute of Community Medicine, University of Tsukuba; Dr. Heizo Tanaka, Medical Research Institute, Tokyo Medical and Dental University; Dr. Shigeru Hisamichi, Tohoku University Graduate School of Medicine; Dr. Masahiro Nakao, Kyoto Prefectural University of Medicine; Dr. Takaichiro Suzuki, Research Institute, Osaka Medical Center for Cancer and Cardiovascular Diseases; Dr. Tsutomu Hashimoto, Wakayama Medical University; Dr. Teruo Ishibashi, Asama General Hospital; and Dr. Katsuhiro Fukuda, Kurume University School of Medicine.

References

Adami HO, Chow W-H, Nyren O, et al (1996). Excess risk of primary liver cancer in patients with diabetes mellitus. *J Natl Cancer Inst*, **88**, 1472-7.

Adami HO, McLaughlin J, Ekbom A, et al (1991). Cancer risk in patients with diabetes mellitus. *Cancer Causes Control*, **2**, 307-14.

Balkau B, Kahn HS, Courbon D, Eschwege E, Ducimetiere P (2001). Hyperinsulinemia predicts fatal liver cancer but is inversely associated with fatal cancer at some other sites. *Diabetes Care*, **24**, 843-9.

Batty GD, Shipley MJ, Marmot M, Smith GD (2004). Diabetes status and post-load plasma glucose concentration in relation to site-specific cancer mortality: findings from the Whitehall study. *Cancer Causes Control*, **15**, 873-81.

Cerhan JR, Wasslace RB, Folsom AR, et al (1997). Medical history risk factors for non-Hodgkin's lymphoma in older women. *J Natl Cancer Inst*, **89**, 314-8.

Cortez-Pinto H, Chatham J, Chacko VP, Arnold C, Rashid A, Diehl AM (1999). Alterations in liver ATP homeostasis in human nonalcoholic steatohepatitis: a pilot study. *J Am Med Assoc (JAMA)*, **282**, 1659-64.

Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ (2004). Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. *Am J Epidemiol*, **159**, 1160-7.

Der G, Everitt BS (2001). A Handbook of Statistical Analysis Using SAS. Second Edition. Chapman & Hall/CRC: New York

El-Serag HB, Tran T, Everhart JE (2004). Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology*, **126**, 460-8.

Fisher WE (2001). Diabetes: risk factor for the development of pancreatic cancer or manifestation of the disease? *World J Surg*, **25**, 503-8.

Fujino Y, Mizoue T, Tokui N, Yoshimura T (2001). Prospective study of diabetes mellitus and liver cancer in Japan. *Diabetes Metab Res Rev*, **17**: 374-9.

Hall GC, Roberts CM, Boulis M, Mo J, Macrae KD (2005). Diabetes and the risk of lung cancer. *Diabetes Care*, **28**, 590-4.

Health and Welfare Statistics Association (2002) Kokumin eisei no doko, 2000 (Trends in nation's health, 2002). Tokyo: Kosei No Shihyo (in Japanese).

Hjalgrim H, Frisch M, Ekbom A, Kyvik KO, Melbye M, Green A (1997). Cancer and diabetes-a follow-up study of two population-based cohorts of diabetes patients. *J Intern Med*, **241**, 471-5.

Hu FB, Manson JE, Liu S, et al (1999). Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women. *J Natl Cancer Inst*, **91**, 542-7.

International Union for Health Promotion and Education (2000). Health promotion effectiveness-the questions to be answered. The evidence of health promotion effectiveness: shaping public health in a new Europe, Part two, p.1-11. IUHPE: Brussels-Luxembourg.

Islam MM, Horibe H, Kobayashi F (1999). Current trend in prevalence of diabetes mellitus in Japan, 1964-1992. *J Epidemiol*, **9**, 155-62.

Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM (2005). Fasting serum glucose level and cancer risk in Korean men and women. *J Am Med Assoc*, **293**, 194-202.

Kaido T, Honda Y, Kitamura K (2002) Association of liver dysfunction and hyperglycemia in Japanese male workers at printing and papermaking plants. *J Occup Health*, **44**, 301-6.

Khan MMH, Saito S, Takagi S, et al (2006). Relationship between hepatocellular carcinoma and impaired glucose tolerance among Japanese. *Hepatogastroenterology*, **53**, 734-8.

Kojima M, Wakai K, Tokudome S, et al (2004). Bowel movement frequency and risk of colorectal cancer in a large cohort study of Japanese men and women. *Br J Cancer*, **90**, 1397-401.

Koskinen SVP, Reunanen ARS, Martelin TP, Valkonen T (1998). Mortality in a large population-based cohort of patients with drug-treated diabetes mellitus. *Am J Public Health*, **88**, 765-70.

Lagiou P, Kuper H, Stuver SO, Tzonou A, Trichopoulos D, Adami HO (2000). Role of diabetes mellitus in the etiology of Hepatocellular carcinoma. *J Natl Cancer Inst*, **92**, 1096-99.

La Vecchia C, Negri E, Decarli A, Franceschi S (1997). Diabetes mellitus and the risk of primary liver cancer. *Int J Cancer*, **73**, 204-7.

La Vecchia C, Negri E, Decarli A, Franceschi S (1997a). Diabetes mellitus and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev*, **6**, 1007-10.

La Vecchia C, Negri E, Franceschi S, D'Avanzo B, Boyle P (1994). A case-control study of diabetes mellitus and cancer risk. *Br J Cancer*, **70**, 950-3.

Limburg PJ, Anderson KE, Johnson TW, et al (2005). Diabetes mellitus and subsite-specific colorectal cancer risks in the Iwoa women's health study. *Cancer Epidemiol Biomarkers Prev*, **14**, 133-7.

Mori M, Saito S, Takagi S, et al (2000). A review of cohort studies on the association between history of diabetes mellitus and occurrence of cancer. *Asian Pacific J Cancer Prev*, **1**, 269-76.

Mori M, Sakauchi F, Washio M, et al (2005). Survey of incidence of cancer as a measure of outcome in the JACC Study. *J Epidemiol*, **15 Suppl 1**, S80-S85.

Natazuka T, Manabe Y, Kono M, Murayama T, Matsui T, Chihara K (1994). Association between non-insulin dependent diabetes mellitus and non-Hodgkin's lymphoma. *Br Med J*, **309**, 1269.

Neil A (2003) Diabetes and cardiovascular disease. *Diabetes Obes Metab*, **5 Suppl 1**, S11-S18.

Ohno Y, Tamakoshi A, and the JACC study group (2001). Japan Collaborative Cohort Study of cancer risk sponsored by Monbusho (JACC Study). *J Epidemiol*, **11**, 144-50.

Saydah SH, Loria CM, Eberhardt MS, Brancati FL (2003). Abnormal glucose tolerance and the risk of cancer death in the United States. *Am J Epidemiol*, **157**, 1092-1100.

Shibata A, Ogimoto I, Kurozawa Y, et al (2003). Past medical history and risk of death due to hepatocellular carcinoma, univariate analysis of JACC Study data. *Kurume Med J*, **50**, 109-19.

Silverman DT, Schiffman M, Everhart J, et al (1999). Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. *Br J Cancer*, **80**, 1830-7.

Smith GD, Egger M, Shipley MJ, Marmot MG (1992). Post-challenge glucose concentration, impaired glucose tolerance, diabetes, and cancer mortality in men. *Am J Epidemiol*, **136**, 1110-4.

Sonoda T, Ishida T, Mori M, et al (2005). A case-control study of multiple myeloma in Japan: association with occupational factors. *Asian Pacific J Cancer Prev*, **6**, 33-6.

Toyoda H, Kumada T, Nakano S, et al (2001). Impact of diabetes mellitus on the prognosis of patients with hepatocellular carcinoma. *Cancer*, **91**, 957-63.

Wideroff L, Gridley G, Mellemkjaer L, et al (1997). Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. *J Natl Cancer Inst*, **89**, 1360-5.

Yoshizawa H (2002). Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. *Oncology*, **62 (suppl 1)**, 8-17.

Zahm SH, Blair A, Cantor KP, Fraumeni JF Jr (1995) Non-insulin dependent diabetes mellitus and non-Hodgkin's lymphoma. Other American studies fail to confirm an association. *Br Med J*, **310**, 1009-10.

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

Yo Sasaki, MD, Terumasa Yamada, MD,* Hideo Tanaka, MD,† Hiroaki Ohigashi, MD,* Hidetoshi Eguchi, MD,* Masahiko Yano, MD,* Osamu Ishikawa, MD,* and Shingi Imaoka, MD**

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.

(*Ann Surg* 2006;244: 771–780)

From the Departments of *Surgery and †Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan.

Reprints: Yo Sasaki, MD, PhD, Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3, Nakamichi, Higashinari-ku, Osaka, 537-8511, Japan. E-mail sasaki-yo@mc.pref.osaka.jp.

ISSN: 0003-4932/06/24405-0771
DOI: 10.1097/01.sla.0000225126.56483.b3

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

	HB-HCC		HC-HCC		
Characteristic	**%**	**No.**	**%**	**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/I)					
<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

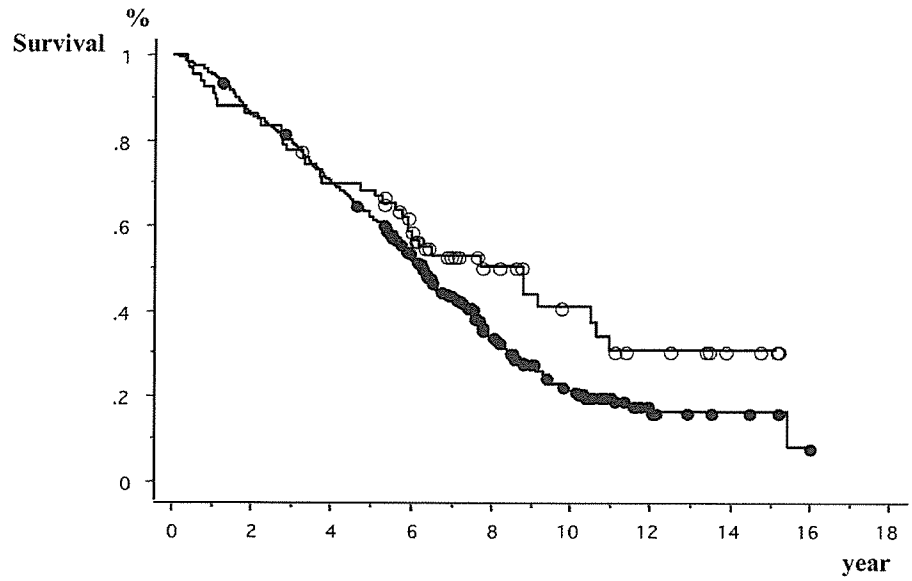

FIGURE 1. Comparison of survivals between patients with hepatitis-B-related hepatocellular carcinoma (HCC) and patients with hepatitis-C-related HCC. Open circles, hepatitis B-related HCC patients (n = 66). Closed circles, hepatitis C-related HCC patients (n = 351). Log-rank test: $P = 0.068$.

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

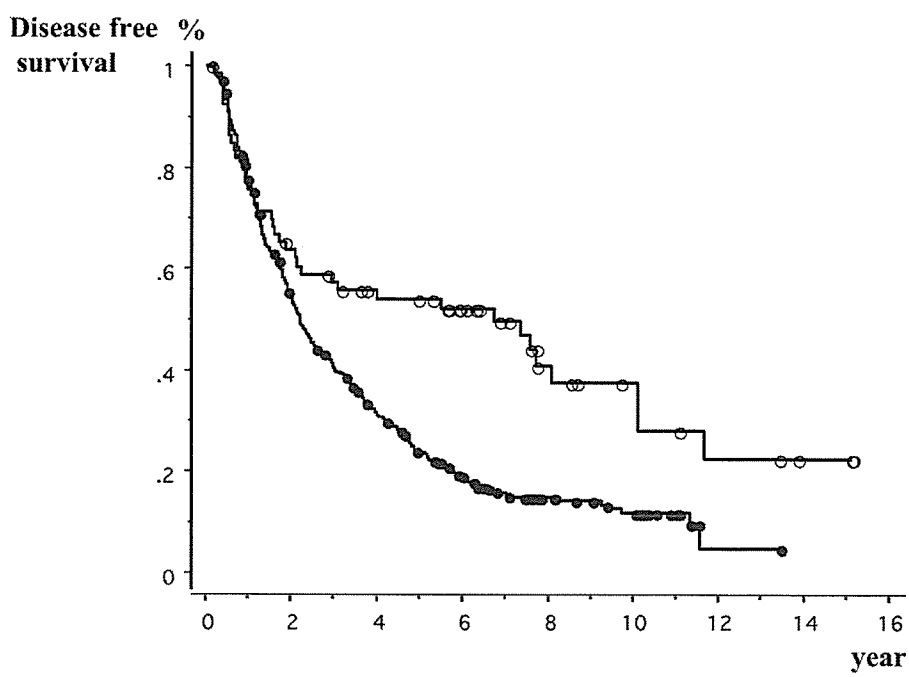

FIGURE 2. Comparison of disease-free survivals between patients with hepatitis-B-related hepatocellular carcinoma (HCC) and patients with hepatitis-C-related HCC. Open circles, hepatitis B-related HCC patients (n = 66). Closed circles, hepatitis C-related HCC patients (n = 351). Log-rank test: $P = 0.0001$.

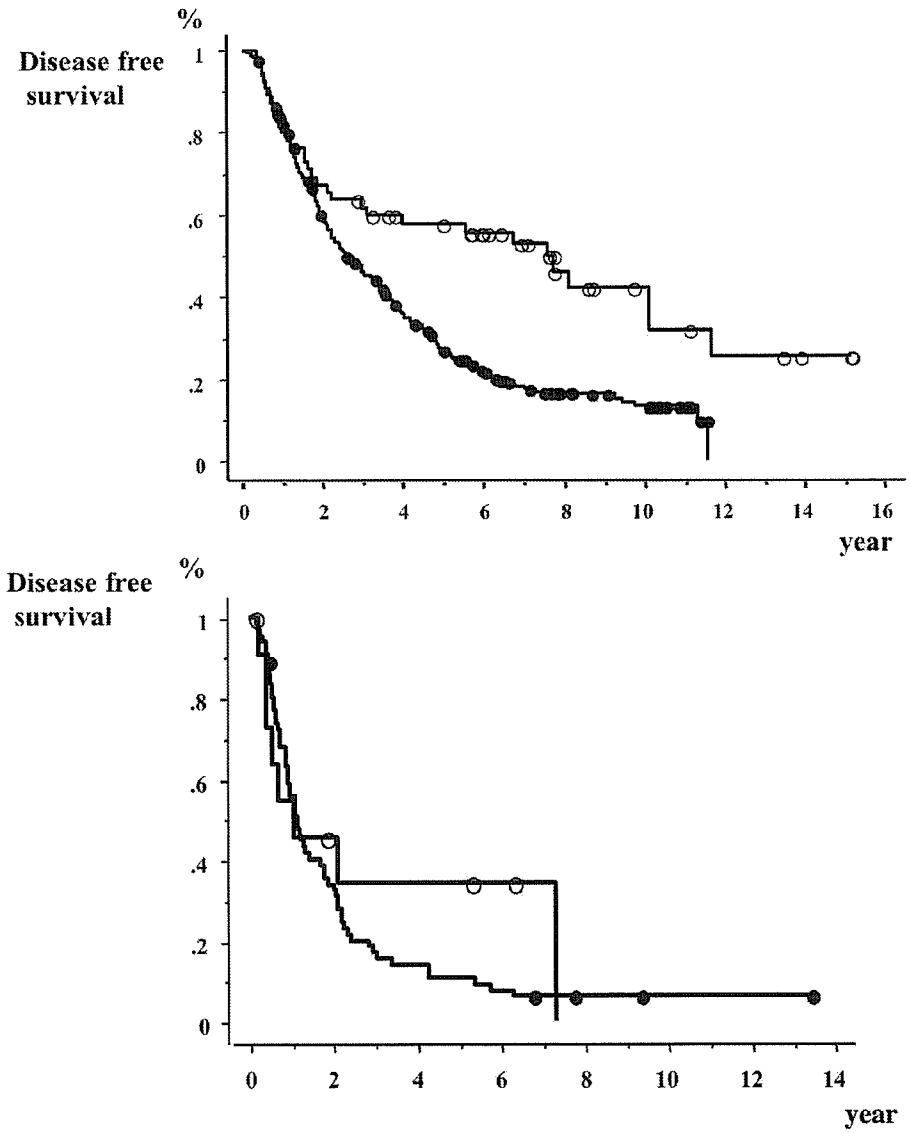

FIGURE 3. Comparison of disease-free survivals between patients with hepatitis-B-related hepatocellular carcinoma (HCC) and patients with hepatitis-C-related HCC in TNM Stages by Liver Cancer Study Group of Japan. Top, stages I and II. Open circles, hepatitis-B-related HCC patients (n = 54). Closed circles, hepatitis-C-related HCC patients (n = 285). Log-rank test: P = 0.0002. Bottom, stages III and IV. Open circles, hepatitis-B-related HCC patients (n = 12). Closed circles, hepatitis-C-related HCC patients (n = 66). Log-rank test: P = 0.42.

stages I and II, the DFS of the HC-HCC group was significantly lower than that of the HB-HCC group, and the DFS of the two groups were remarkably different 2 years after surgery and later. In contrast, there were no significant differences between the DFS of the two groups in stages III and IV. In the comparison of Child's classification, both in Child's A and in Child's B + C, the DFS of the HC-HCC group was lower than that of the HB-HCC group, especially 2 years after surgery and later.

Univariate and Multivariate Analysis for DFS of HCC Patients Who Underwent Hepatic Resection

Univariate analysis and unadjusted hazard ratios for DFS were calculated on the HCC patients who underwent hepatic resection (Table 3). The risk of recurrence from HCC was 1.92 times greater in HC-HCC patients than in HB-HCC patients (P = 0.002, 95% confidential interval [CI], 1.37–2.70). In the other factors, ALT and ICG-R15 were selected from the clinical factors for DFS. From tumor factors: tumor size, number of tumors, and TNM stage by LCSGJ; from surgical factors: operation time, blood loss, perioperative transfusion, and surgical margin; and from pathologic factors: histologic grade (Edmondson's grade), extracapsular invasion, satellite nodules, and venous invasion were significantly strong predicators of risk for recurrence.

Multivariate analysis was performed for DFS using the selected variables of which the P values were less than 0.05 in univariate analysis (Table 4). Viral hepatitis was chosen for a serologic factor, and ALT was chosen from hepatic inflammatory activity factors, ICG-R15 from hepatic functional reserve factors, and from tumor factors TNM stage by LCSGJ, which includes the factors of both tumor size and tumor number. Blood loss and surgical margin were selected from operative factors, and Edmondson's grade, extracapsular invasion, and venous invasion from pathologic factors. As a result, viral hepatitis was one of the independent prognostic factors for DFS together with

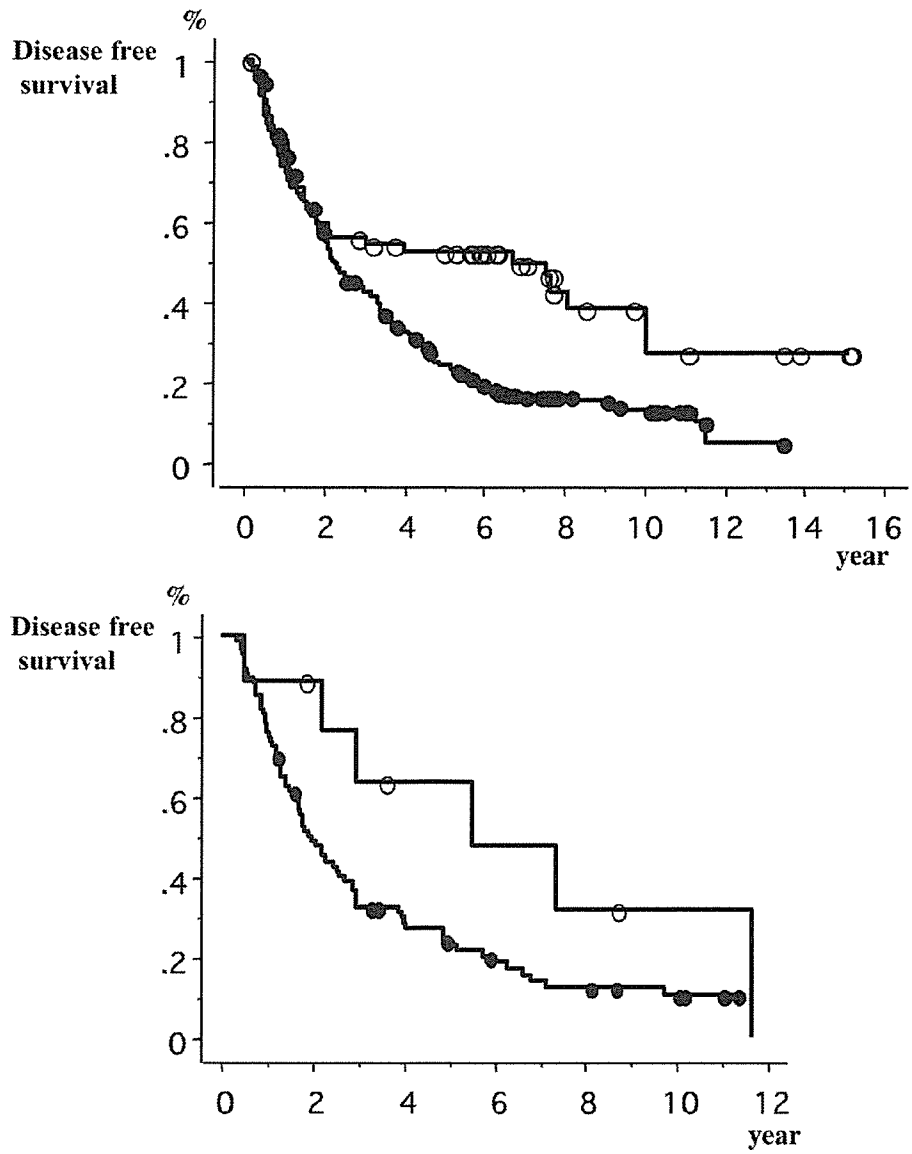

FIGURE 4. Comparison of disease-free survivals between patients with hepatitis-B-related hepatocellular carcinoma (HCC), and hepatitis-C-related HCC using Child's classification. Top, Child's A. Open circles, hepatitis-B-related HCC patients (n = 57). Closed circles, hepatitis-C-related HCC patients (n = 261). Log-rank test: P = 0.001. Bottom, Child's B + C; Open circles, hepatitis-B-related HCC patients (n = 9). Closed circles, hepatitis-C-related HCC patients (n = 90). Log-rank test: P = 0.06.

TNM stage, surgical margin, and Edmondson's grade (P = 0.002). The risk of recurrence from HCC increased to 1.93 times greater in HC-HCC patients than in HB-HCC patients after adjustment and the 95% CI became 1.27 to 2.93. When the patients whose first recurrence was distant metastasis were accounted for censored cases at the time of discovering the metastasis, the adjusted hazard ratio for the viral types was not changed (hazard ratio, 2.11; 95% CI, 1.36–3.28).

DISCUSSION

The findings about the differences of various kinds of clinicopathologic characters such as age, hepatic inflammatory activity, liver functional reserve, and tumor and operative factors, etc., between HB-HCC and HC-HCC patients, which we indicated in this study, were consistent with those in previous reports for the most part[17,22] (Table 2). On the other hand, the opinions about the differences of long-term clinical course after hepatic resection of the two groups were controversial. Takenaka et al[17] reported the comparison of the outcome of a total of 126 patients with HB- or HC-HCC who underwent hepatic resection, and described that the survival and DFS at 5 years were similar in both groups. Similarly, some other reports described that long-term prognosis was not influenced by hepatitis virus types.[23–26] On the other hand, Wu et al[7] reported that the DFS rates between the two groups were not significantly different, but that the survival of HB-HCC patients was significantly lower than that of HC-HCC patients. They described that the poorer prognosis in HB-HCC patients was caused by a higher incidence of poor prognostic characters in the HB-HCC group. Haratake et al[27] similarly reported that the prognosis of HB-HCC patients was worse than that of HC-HCC patients. These inconsistent findings possibly resulted from insufficient number of patients and follow-up periods for satisfactory analysis. We

TABLE 3. Univariate Analysis and Unadjusted Hazard Ratios of Prognostic Factors for Disease-Free Survival on HCC Patients Who Underwent Hepatic Resection

			DFS Rate (%)				
	No. of Patients	**50% DFS (yr)**	**5 yr**	**10 yr**	***P* Value**	**Hazard Ratio**	**95% CI**
Viral hepatitis							
B type	66†	6.73†	54†	38†		1.00 (Reference)†	
C type	351†	2.21†	24†	12†	0.002†	1.92†	1.37–2.70†
Age (yr)							
≤65	298	2.43	30	17		1.00 (Reference)	
>65	119	2.10	27	13	0.28	1.14	0.90–1.46
Gender							
Male	317	2.30	29	15		1.00 (Reference)	
Female	100	2.23	26	20	0.92	1.01	0.78–1.31
ALT (U/l)							
<80	227†	2.43†	32†	21†		1.00 (Reference)†	
≥80	190†	2.21†	24†	9†	0.03†	1.28†	1.02–1.59†
Alb (g/dL)							
≥3.5	320	2.37	30	18		1.00 (Reference)	
<3.5	97	2.22	26	10	0.20	1.18	0.92–1.52
T bil (mg/dL)							
<1.0	291	2.45	31	17		1.00 (Reference)	
≥1.0	126	2.09	25	14	0.24	1.16	0.91–1.47
ICG-R15 (%)*							
<20	249†	2.55†	33†	20†		1.00 (Reference)†	
≥20	161†	2.10†	25†	11†	0.03†	1.29†	1.03–1.62†
Prothrombin time (%)							
>80	327	2.28	30	17		1.00 (Reference)	
≤80	90	2.43	24	13	0.74	1.05	0.80–1.38
Child's classification							
A	317	2.37	30	18		1.00 (Reference)	
B + C	98	2.21	27	12	0.26	1.16	0.90–1.49
Preoperative TAE							
No	272	2.36	32	20		1.00 (Reference)	
Yes	145	2.37	25	12	0.30	1.13	0.89–1.44
AFP (ng/mL)							
≤100	245	2.45	29	9		1.00 (Reference)	
>100	172	1.82	27	20	0.47	1.10	0.85–1.41
Tumor size (cm)							
≤3.0	256†	2.89†	33†	19†		1.00 (Reference)†	
>3.0	161†	1.63†	21†	9†	0.0002	1.52†	1.22–1.90†
No. of tumors							
1	318†	2.97†	33†	20†		1.00 (Reference)†	
2 or more	99†	1.42†	15†	6†	<0.0001†	1.92†	1.50–2.46†
TNM stage by LCSGI							
I + II	339†	2.95†	32†	19†		1.00 (Reference)†	
III + IV	88†	1.13†	14†	7†	<0.0001†	2.05†	1.58–2.66†
Operation time (mm)							
≤180	135†	3.00†	34†	22†		1.00 (Reference)†	
>180†	282†	2.11†	26†	13†	0.01†	1.35†	1.06–1.72†
Blood loss (ml)							
≤1000	210†	3.00†	33†	19†		1.00 (Reference)†	
>1000	207†	2.08†	24†	13†	0.02†	1.31†	1.05–1.63†
Surgical margin (mm)							
≥10	176†	3.46†	34†	19†		1.00 (Reference)†	
<10	241†	2.01†	25†	14†	0.002†	1.42†	1.13–1.77†

(Continued)

TABLE 3. *(Continued)*

	No. of Patients	50% DFS (yr)	DFS Rate (%) 5 yr	DFS Rate (%) 10 yr	*P* Value	Hazard Ratio	95% CI
Transfusion							
No	233†	2.85†	33†	20†		1.00 (Reference)†	
Yes	184†	1.93†	23†	11†	0.01†	1.32†	1.06–1.64†
Resection range							
Hr0 + Hr5	262	2.37	29	16		1.00 (Reference)	
Hr1 + Hr2 + Hr3	155	2.13	28	16	0.88	1.03	0.82–1.29
Edmondson's grade							
I	79†	3.98†	40†	19†		1.00 (Reference)†	
II + III	262†	1.93†	24†	15†	0.005†	1.53†	1.14–2.06†
Extracapsular invasion							
No	161†	3.09†	33†	18†		1.00 (Reference)†	
Yes	186†	1.80†	23†	15†	0.005†	1.41†	1.11–1.79†
Satellite nodule							
No	242†	2.66†	29†	17†		1.00 (Reference)†	
Yes	94†	1.33†	24†	14†	0.02†	1.44†	1.10–1.87†
Venous invasion							
No	210†	2.57†	30†	17†		1.00 (Reference)†	
Yes	130†	1.42†	23†	14†	0.02†	1.33†	1.04–1.70†
Noncancer tissue							
Normal or fibrosis	145	2.36	33	26		1.00 (Reference)	
Corrhosis	272	2.21	28	11	0.08	1.28	0.97–1.68

HCC, hepatocellular carcinoma; DFS, disease-free survival; ICG R 15, indocyanine green 15 min retention test (normal ≤10%); AFP, alpha fetoprotein; TAE, transarterial embolization; Hr0, partial resection; HrS, subsegmentectomy; Hr1, one segmentectomy; Hr2, two segmentectomy; Hr3, three segmentectomy; LCSGJ, Liver Cancer Study Groups 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.

†Factor with significant differences.

have shown the difference of hepatitis viral type had a dramatic impact on long-term DFS after surgery by a long follow-up period and a large number of patients (Fig. 2). If the follow-up period of our study was short and the comparative study was only about survivals, as the survivals of the two groups were almost the same until 7 years after surgery even in our study, our conclusions might be similar to previous reports,[23–26] which stated hepatitis virus type was not influential in long-term prognosis.

In both the HB-HCC and HC-HCC groups, the recurrence curves were steep for the first 2 years. Afterward, though the curve of the HB-HCC group became very gentle, ie, the recurrence rate decreased dramatically, that of the HC-HCC group kept going down until 7 years after surgery, ie, the recurrence rate remained high during the later years (Fig. 2). The recurrences in the early period after surgery were considered to be mostly attributed to intrahepatic metastasis in both the HB-HCC and HC-HCC groups,[28] whereas the recurrences occurring in the later follow-up years after surgery in the HC-HCC group can be presumed to have been caused by the higher frequency of metachronous carcinogenesis.[29] We showed HC-HCC had the stronger hepatic inflammatory activity shown by the higher level of ALT, and the poorer liver functional reserve shown by the worse grade of Child's classification (Table 2). These findings are regarded to be the high-risk factors of developing HCC. However, even in the same liver function subgroup, which was separated based on Child's classification categorizing the degree of liver function, the potential of recurrence in the later follow-up years was stronger in the HC-HCC group than in the HB-HCC group regardless of the grade of liver functional reserve (Fig. 4). In addition, multivariate analysis showed that the difference of viral hepatitis itself was one of the independent prognostic factors for risk of recurrence (Table 4). These data may suggest that the high frequency of recurrence due to metachronous carcinogenesis in HC-HCC patients is caused not only by the high inflammatory activity or poor functional reserve but also by the other etiologic pathway induced by chronic HCV infection. Takano et al[30] reported that the incidence of HCC in chronic hepatitis C patients was 2.7 times higher than that in chronic hepatitis B patients. Ikeda et al[31] described that the incidence rates of HCC in HC patients and HB patients were 4.8% and 2.1% at the 5th year, 13.6% and 4.9% at the 10th year, respectively, and that the rates showed significant differences.

Even in earlier stages, such as TNM stages I and II, the recurrence rates of HC-HCC continued increasing until the later follow-up years, although the rates of HB-HCC decreased 2 years after surgery and later (Fig. 3, top). On the other hand, in more advanced stages, such as TNM stages III and IV, most recurrences happened in the early follow-up years in both HC-HCC and HB- HCC patients (Fig. 3,

TABLE 4. Multivariate Analysis and Adjusted Hazard Ratios of Prognostic Factors for Disease-Free Survival on HCC Patients Who Underwent Hepatic Resection

Variable	No. of Patients	Hazard Ratio	95% CI	*P*
Viral hepatitis				
B type:C type	66:351†	1.93†	1.27–2.93†	0.002†
ALT (u/l)				
<80:≥80	227:190	1.14	0.87–1.49	0.36
ICG R15 (%)*				
<20:≥20	249:161	1.17	0.69–1.49	0.25
TNM stage by LCSGJ				
I + II:III + IV	339:88†	2.15†	1.55–2.97†	<0.0001†
Blood loss (ml)				
≤1000:≥1000	210:207	1.22	0.89–1.66	0.20
Surgical margin (mm)				
≥10:<10	176:241†	1.34†	1.00–1.80†	0.049†
Edmondson's grade				
I:II + III	79:262†	1.48†	1.01–2.15†	0.04†
Extracapsular invasion				
No:yes	161:186	1.06	0.78–1.45	0.70
Venous invasion				
No:yes	210:130	1.27	0.95–1.71	0.10

HCC, hepatocellular carcinoma; ICG-R 15, indocyanine green 15-min retention test (normal range ≤10%); LCSGJ, Liver Cancer Study Group of 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.

†Factor with significant differences.

bottom). These findings may suggest that it is necessary to change the treatment strategy for HCC patients not only by the stage of progression or liver function but also the difference of viral hepatitis type. Namely, intrahepatic metastasis is considered to be the main form of recurrence in advanced stages of HCC. Therefore, for the more advanced stages of HCC, such as stages III or IV, regardless of the difference of hepatitis virus, we should pay attention to the appearance of intrahepatic metastasis in the early follow-up years after surgery, and an anticancer therapy such as chemotherapy may be recommended to reduce this type of recurrence. On the other hand, mainly for HC-HCC in less-advanced HCC, such as stages I or II, we should make a close follow-up to check intrahepatic recurrence by multicentricity even 2 years after surgery or later, and antiviral treatment such as interferon with or without ribavirin might be useful for preventing a second primary occurrence.[32]

REFERENCES

1. Choo QL, Kuo G, Weiner AJ, et al. Isolation of a cDNA clone derived from a blood born non-A, non-B virus hepatitis genome. *Science.* 1989;244:359–362.
2. Kuo G, Choo QL, Alter HJ, et al. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. *Science.* 1989;244:362–364.
3. Ikai I, Itai Y, Okita K, et al. Report of the 15th follow-up survey of primary liver cancer. *Hepatol Res.* 2004;28:21–29.
4. Colombo M, Kuo G, Choo QL, et al. Prevalence of antibodies to hepatitis C virus in Italian patients with hepatocellular carcinoma. *Lancet.* 1989;2:1006–1008.
5. Bruix J, Barrera JM, Calvet X, et al. Prevalence of antibodies to hepatitis C virus in Spanish patients with hepatocellular carcinoma and hepatic cirrhosis. *Lancet.* 1989;2:1004–1006.
6. Tsai JF, Chang WY, Jeng JE, et al. Hepatitis B and C virus infection as risk factors for liver cirrhosis and cirrhotic hepatocellular carcinoma: a case-control study. *Liver.* 14:98–102.
7. Wu CC, Ho WL, Chen JT, et al. Hepatitis viral status in patients undergoing liver resection for hepatocellular carcinoma. *Br J Surg.* 1999;86:1391–1396.
8. Shim J, Kim BH, Kim NH, et al. Clinical features of HBsAg-negative but anti-HBc-positive hepatocellular carcinoma in a hepatitis B virus endemic area. *J Gastroenterol Hepatol.* 2005;20:746–751.
9. Szmuness W. Hepatocellular carcinoma and the hepatitis B virus: evidence for a causal association. *Prog Med Virol.* 1978;24:40–69.
10. Beasley RP, Hwang LY, Lin CC, et al. Hepatocellular carcinoma and hepatitis B virus. *Lancet.* 1981;2(suppl):1129–1133.
11. Okuda K. Hepatocellular carcinoma: recent progress. *Hepatology.* 1992; 15:948–963.
12. Brechot C, Poucel C, Louise A, et al. Presence of integrated hepatitis B virus DNA sequences in cellular DNA of human hepatocellular carcinoma. *Nature.* 1980;286:533–535.
13. Shafritz DA, Kew MC. Identification of integrated hepatitis B virus DNA sequences in human hepatocellular carcinomas. *Hepatology.* 1981; 1:1–8.
14. Kim CM, Koike K, Saito I, et al. HBx gene of hepatitis B virus induces liver cancer in transgenic mice. *Nature.* 1991;351:317–320.
15. Sherlock S. Viruses and hepatocellular carcinoma. *Gut.* 1994;35:828–832.
16. Tanabe G, Nuruki K, Baba Y, et al. A comparison of hepatocellular carcinoma associated with HBV or HCV infection. *Hepatogastroenterology.* 1999;46:2442–2446.
17. Takenaka K, Yamamoto K, Taketomi A, et al. A comparison of the surgical results in patients with hepatitis B versus hepatitis C-related hepatocellular carcinoma. *Hepatology.* 1995;22:20–24.
18. Pugh RNH, Murray-Lyon IM, Dawson JL. Transection of the esophagus for bleeding esophageal varices. *Br J Surg.* 1973;60:646–669.
19. Liver Cancer Study Group of Japan. *The General Rules for the Clinical and Pathological Study of Primary Liver Cancer,* 2nd English ed. Tokyo: Kanehara, 2003.
20. Henderson JM, Sherman M, Tavill A, et al. AHPBA/AJCC consensus conference on staging of hepatocellular carcinoma: consensus statement. *J Hepatobiliary Pancreat Surg.* 2003;5:243–250.
21. Edondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,000 necropsies. *Cancer.* 1954;7:462–502.
22. Chen MF, Jeng LB, Lee WC. Surgical results in patients with hepatitis virus-related hepatocellular carcinoma in Taiwan. *World J Surg.* 2002; 26:742–747.
23. Chen MF, Jeng LB, Lee WC, et al. Surgical results in patients with dual hepatitis B- and C-related hepatocellular carcinoma compared with hepatitis B- or hepatitis C-related hepatocellular carcinoma. *Surgery.* 1998;123:554–559.
24. Miyagawa S, Kawwasaki S, Makuuchi M. Comparison of the characteristics of hepatocellular carcinoma between hepatitis B and hepatitis C viral infection: tumor multicentricity in cirrhotic liver with hepatitis C. *Hepatology.* 1996;24:307–310.
25. Shiraishi M, Hiroyasu S, Nagahama M, et al. Characteristics of hepatocellular carcinoma in patients with negative virus markers: clinicopathologic study of resected tumors. *World J Surg.* 1999;23:301–305.
26. Yamanaka N, Tanaka T, Tanaka W, et al. Correlation of hepatitis virus serologic status with clinicopathologic features in patients undergoing hepatectomy for hepatocellular carcinoma. *Cancer.* 1997;79:1509–1515.
27. Haratake J, Takeda S, Kasai T, et al. Predictable factors for estimating prognosis of patients after resection of hepatocellular carcinoma. *Cancer.* 1993;72:1178–1183.
28. Sakon M, Umeshita K, Nagano H, et al. Clinical significance of hepatic resection in hepatocellular carcinoma: analysis by disease-free survival curves. *Arch Surg.* 2000;135:1456–1459.
29. Sasaki Y, Imaoka S, Masutani S, et al. Influence of coexisting cirrhosis

on long-term prognosis after surgery in patients with hepatocellular carcinoma. *Surgery*. 1992;112:515–521.
30. Takano S, Yokosuka O, Imazeki F, et al. Incidence of hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. *Hepatology*. 1995;21:650–655.
31. Ikeda K, Saitoh S, Suzuki Y, et al. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. *J Hepatol*. 1998;28:930–938.
32. Kubo S, Nishiguchi S, Hirohashi K, et al. Effect of long-term postoperative interferon-alpha therapy on intrahepatic recurrence after resection of hepatitis C virus-related hepatocellular carcinoma: a randomized, controlled trial. *Ann Intern Med*. 2001;134:963–967.

ELSEVIER

Atherosclerosis 190 (2007) 216–223

ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort

Tomonori Okamura[a,*], Hideo Tanaka[b], Naomi Miyamatsu[c], Takehito Hayakawa[d], Takashi Kadowaki[a], Yoshikuni Kita[a], Yasuyuki Nakamura[e], Akira Okayama[f], Hirotsugu Ueshima[a], for the NIPPON DATA80 research group[1]

[a] *Department of Health Science, Shiga University of Medical Science, Shiga, Japan*
[b] *Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan*
[c] *Department of Clinical Nursing, Shiga University of Medical Science, Shiga, Japan*
[d] *Department of Public Health, Shimane University School of Medicine, Shimane, Japan*
[e] *Cardiovascular Epidemiology, Faculty of Home Economics, Kyoto Womens's University, Kyoto, Japan*
[f] *Department of Preventive Cardiology, National Cardiovascular Center, Osaka, Japan*

Received 29 August 2005; received in revised form 4 January 2006; accepted 25 January 2006
Available online 10 March 2006

Abstract

No study has shown a positive relationship between hypercholesterolemia and all-cause mortality in the Japanese population. Therefore, a cohort study of 17.3 years' duration was conducted on 9216 participants aged 30 years or older, selected randomly from throughout Japan. In both the lowest (<4.14 mmol/L, 160 mg/dl) and highest (≥6.71 mmol/L, 260 mg/dl) total cholesterol (TC) groups, there was a positive association between TC and risk of all-cause mortality (hazard ratio (HR) 1.19; 95% confidence interval (CI), 1.03–1.37 and 1.36 (95% CI, 1.05–1.77), respectively). The lowest TC group had an increased risk of liver disease (HR 3.03; 95% CI, 1.70–5.43), whereas the highest TC group had an increased risk of coronary heart disease (HR 3.81; 95% CI, 1.70–5.43). After exclusion of deaths due to liver disease during the entire follow-up period and all-cause deaths within the first 5 years of follow-up, the increased HR in the lowest TC group disappeared (HR 1.05; 95% CI, 0.89–1.24). Although the cut-off point seemed to be higher than that for Western populations, hypercholesterolemia was shown to be positively associated with all-cause mortality in Japan.

Keywords: Cholesterol; All-cause mortality; Liver disease; Cohort studies; Risk factors

* Corresponding author at: Department of Health Science, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu, Shiga 520-2192, Japan. Tel.: +81 77 548 2191; fax: +81 77 543 9732.
E-mail address: tokamura@belle.shiga-med.ac.jp (T. Okamura).

[1] Members of the NIPPON DATA80 Research group are listed in [Okamura T, Kadowaki T, Hayakawa T, et al. What cause of mortality can we predict by cholesterol screening in the Japanese general population? J Intern Med 2003;253:169–80; Okamura T, Hayakawa T, Kadowaki T, et al. Resting heart rate and cause-specific death in a 16.5-year cohort study of the Japanese general population. Am Heart J 2004;147:1024–32; Ueshima H, Choudhury SR, Okayama A, et al. Cigarette smoking as a risk factor for stroke death in Japan: NIPPON DATA80. Stroke 2004;35:1836–41; Okamura T, Hayakawa T, Kadowaki T, et al. A combination of serum low albumin and above-average cholesterol level was associated with excess mortality. J Clin Epidemiol 2004;57:1188–95; Nakamura Y, Okamura T, Tamaki S, et al. Egg consumption, serum cholesterol, and cause-specific and all-cause mortality: the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980 (NIPPON DATA80). Am J Clin Nutr 2004;80:58–63; Miyamatsu N, Kadowaki T, Okamura T, et al. Different effects of blood pressure on mortality from stroke subtypes depending on BMI levels: a 19-year cohort study in the Japanese general population, NIPPON DATA80. J Hum Hypertens 2005;19:285–91; Nakamura Y, Ueshima H, Okamura T, et al. Association between fish consumption and all-cause and cause-specific mortality in Japan: NIPPON DATA80, 1980–1999. Am J Med 2005;118:239–45].

0021-9150/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2006.01.024

1. Introduction

The causal relationship between high levels of serum total cholesterol (TC) and coronary heart disease is well established. Several studies in Western populations have shown clearly that a high cholesterol concentration contributes to an increased risk of all-cause mortality [1–4]. However, to our knowledge, a positive relationship between high serum levels of TC and all-cause mortality has not been reported in Asian populations [5–8].

Recent prospective studies in Japan have shown, however, that low serum TC is a predictive marker for deaths due to liver cancer in community residents [8] and for liver cancer in blood donor who are positive for antibodies to the hepatitis C virus [9]. Accordingly, the relationship between TC and all-cause mortality may be affected by liver diseases in the Japanese population, which is known to have a higher mortality from chronic liver diseases and liver cancer compared with Western populations [10].

Therefore, our a priori hypothesis was that serum TC may be associated positively with all-cause mortality in Japanese residents, but that this relationship may be modified by mortality from liver disease. In order to investigate the validity of this hypothesis, we carried out a 17.3-year cohort study to investigate the relationship between serum TC and all-cause and/or liver disease mortality.

2. Methods

2.1. Populations

A total of 10,546 community dwellers (4640 men and 5906 women), aged 30 years and over, from 300 districts participated in the National Cardiovascular Survey in 1980. These districts were randomly selected throughout Japan to avoid regional bias. In other words, this survey covered all 47 prefectures of Japan according to census population in 1980.

These participants were followed until 1999. As the overall population aged ≥30 in the surveyed districts numbered 13,771, the number of participants was 10,546 (participation rate) 76.6%). The present study extended the follow-up period of NIPPON DATA80 (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980), the details of which have been reported previously [8,11–16]. Of the 10,546 participants, a total of 1330 were excluded for the following reasons: past history of coronary heart disease or stroke ($n=280$), missing information at the baseline survey ($n=180$), and lost to follow-up ($n=870$). We then analyzed the data from the remaining 9216 participants (4035 men and 5181 women). There was no significant difference in the mean TC between the participants lost to follow-up and those in the study.

2.2. Endpoint determination

As reported previously, [8,11–16] we confirmed those participants who had died in each area by computer matching of data from the National Vital Statistics, using the area, gender, date of birth and death as key codes. In order to clarify the cause of death, we used the National Vital Statistics. In Japan, all death certificates issued by medical doctors are forwarded centrally to the Ministry of Health and Welfare via the public health centers in the area of residency. The underlying cause of death for the National Vital Statistics was coded according to the Ninth International Classification of Disease (ICD-9) until the end of 1994 and from the beginning of 1995 by the 10th International Classification of Disease (ICD-10) by specialists for coding in the Ministry of Health and Welfare. In our analyses, liver cancer (ICD-9 code: 155, 199.1; ICD-10 code: C22) and non-cancer liver disease (ICD-9 code: 70, 570–573; ICD-10 code: B15–B19, K70–K77) were combined into a single category (death due to liver disease).

Permission to use the National Vital Statistics was obtained from the Management and Coordination Agency, Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (Nos. 12–18, 2000).

2.3. Baseline examination

Non-fasting blood samples were drawn and centrifuged within 60 min of collection. Serum total cholesterol and albumin were analyzed using an auto analyzer (SMA12/60; Technicon, Tarrytown, USA) at one central laboratory (Present name: Osaka Medical Center for Health Science and Promotion). Since April 1975, the precision and accuracy of the cholesterol measurements in the laboratory have been certified by the CDC-NHLBI Lipid Standardization Program of the Center for Disease Control and Prevention (CDC), Atlanta, Georgia [17].

Baseline blood pressures were measured on the right arm of seated participants by trained observers using a standard mercury sphygmomanometer. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, the use of antihypertensive agents, or any combination of these findings. Serum glucose was measured by the cupric-neocuproine method. Diabetes was defined as a non-fasting serum glucose ≥11.1 mmol/L, a history of diabetes, or both. Height in stocking feet and weight in light clothing were measured. Public health nurses obtained information on smoking, drinking and medical history.

2.4. Statistical analysis

We set the cut-off points for serum TC based on the combination of clinical criteria. First, we defined 4.14 mmol/L (160 mg/dl), 5.18 mmol/L (200 mg/dl) and 6.21 mmol/L (240 mg/dl) of serum TC as cut-off points according to the

adult treatment panel III [18] and international conference of low blood cholesterol [4]. The Japan Atherosclerotic Association also defined 5.69 mmol/L (220 mg/dl) or greater as a threshold criterion for hypercholesterolemia; [19] on the other hand, the manual of Health and Medical Service Law in Japan recommends medication for hypercholesterolemia when serum TC is 6.71 mmol/L (260 mg/dl) or greater [20]. Finally, we added "4.66 mmol/L (180 mg/dl)" as an additional cut-off point because there was a large number of participants with TC levels between 4.14 and 5.17 mmol/L. Consequently, the relationship between serum TC and mortality was determined in the following seven groups with 0.51 mmol/L (20 mg/dl) increments: <4.14 mmol/L (<160 mg/dl), 4.14–4.65 (160–179), 4.66–5.17 (180–199), 5.18–5.68 (200–219), 5.69–6.20 (220–240), 6.21–6.70 (240–259) and ≥6.71 mmol/L (≥260). We used the participants with TC levels between 4.14 and 4.65 mmol/L as a reference group because this was the largest of the seven TC groups. We also used quintiles of serum TC to group the participants (<4.16, 4.16–4.59, 4.60–5.03, 5.04–5.60, ≥5.61 mmol/L).

Age-adjusted mean values and the prevalence of baseline characteristics were estimated using analysis of covariance or the chi-square test. The multivariable adjusted hazard ratio (HR) for all-cause or cause-specific mortality was calculated using a Cox's proportional hazards model adjusted for age, serum albumin, body mass index, hypertension, diabetes, cigarette smoking and alcohol intake. We used three dummy variables to classify subjects based on their smoking habit (never-smoked; ex-smoker; current smoker ≤20 and >20 cigarettes/day, with never-smoked being defined as the reference group) and their alcohol intake (never-drank; ex-drinker; occasional drinker and daily drinker, with never-drank being defined as the reference group). Gender-specific analyses were also carried out.

The analyses were repeated excluding all-cause deaths within the first 5 years of follow-up and/or deaths due to liver disease during the entire follow-up period.

All confidence intervals were estimated at the 95% level and significance was assumed at a P-value of <0.05. The Statistical Package for the Social Sciences (SPSS Japan Inc. version 13.0J, Tokyo, Japan) was used for all the analyses.

3. Results

The mean age in our entire study population was 50.0 ± 13.2 years (mean ± S.D.), 49.7 ± 13.1 years in men and 50.1 ± 13.3 years in women. The mean serum TC was 4.88 ± 0.87 mmol/L (188.6 ± 33.6 mg/dl), 4.81 ± 0.85 mmol/L (186.0 ± 32.9 mg/dl) in men and 4.93 ± 0.88 mmol/L (190.7 ± 34.0 mg/dl) in women.

Table 1 shows the age-adjusted means and prevalence of the baseline characteristics of all the participants in each

Table 1
Age and age-adjusted mean value and prevalences of baseline characteristics stratified by cholesterol level at the baseline survey in 1980, NIPPON DATA80

Risk characteristics	Baseline serum total cholesterol level (mmol/L)							P-values[a]
	<4.14	4.14–4.65	4.66–5.17	5.18–5.68	5.69–6.20	6.21–6.70	6.71-	
Men								
TC, stratum mean (mmol/L)	3.74	4.39	4.91	5.41	5.90	6.41	7.30	
No. of persons	851	1000	937	648	354	167	78	
Age (years)	51.0 (14.0)	50.0 (13.4)	49.3 (13.1)	48.8 (12.6)	48.9 (11.8)	50.2 (12.2)	49.3 (11.0)	<0.001
Albumin (g/L)	43.0 (0.10)	44.1 (0.09)	44.4 (0.09)	45.0 (0.10)	45.4 (0.13)	45.6 (0.22)	45.7 (0.31)	<0.001
BMI (kg/m^2)	21.7 (0.13)	22.0 (0.09)	22.6 (0.09)	23.2 (0.11)	23.5 (0.14)	23.9 (0.21)	24.1 (0.29)	0.030
Hypertension (%)	44.9	46.3	50.3	50.3	55.4	57.5	62.8	<0.001
Diabetes (%)	1.2	0.8	1.2	1.7	1.2	0.6	2.6	0.603
Daily drinker (%)	46.7	49.5	48.9	49.4	48.3	36.5	50	0.081
Current smoker (%)	66.9	66.4	63.9	56.3	59.3	57.5	53.8	<0.001
Heavy smoker (>20 cigarettes day^{-1}) (%)	21.2	24.6	25.1	23.3	30.5	29.3	28.2	0.017
Women								
TC, stratum mean (mmol/L)	3.78	4.40	4.91	5.40	5.91	6.40	7.20	
No. of persons	952	1183	1142	925	528	275	176	
Age (years)	44.7 (12.9)	47.3 (13.0)	50.6 (12.8)	53.1 (12.9)	54.8 (12.0)	56.3 (11.5)	56.9 (11.6)	<0.001
Albumin (g/L)	43.1 (0.08)	43.3 (0.07)	43.6 (0.07)	43.9 (0.08)	44.0 (0.10)	44.0 (0.17)	44.3 (0.19)	<0.001
BMI (kg/m^2)	22.1 (0.10)	22.4 (0.10)	22.8 (0.10)	23.2 (0.11)	23.6 (0.15)	23.8 (0.20)	24.4 (0.30)	<0.001
Hypertension (%)	27.0	32.7	37.5	46.8	54.0	56.4	58.5	<0.001
Diabetes (%)	0.2	0.6	0.6	1.2	1.5	2.2	3.4	<0.001
Daily drinker (%)	3.2	2.6	3.0	2.7	3.2	1.8	2.8	0.920
Current smoker (%)	7.9	7.9	10.1	9.2	11.0	5.5	9.1	0.068
Heavy smoker (>20 cigarettes day^{-1}) (%)	0.7	0.3	0.8	0.6	1.5	0.7	0.6	0.291

[a] Analysis of covariance for continuous variables, chi-square test for categorical variables. The null hypothesis is that each mean or prevalence among all TC categories was equal. Numbers in parentheses are standard deviations for age and standard errors for other variables.