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

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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

*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.

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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.

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.

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