RESEARCH ARTICLE

Diabetes Mellitus and Risk of Colorectal Cancer Mortality in Japan: the Japan Collaborative Cohort Study

Ce Tan[1]*, Mitsuru Mori[1], Yasushi Adachi[2], Kenji Wakai[3], Sadao Suzuki[4], Koji Suzuki[5], Shuji Hashimoto[6], Yoshiyuki Watanabe[7], Akiko Tamakoshi[8]

Abstract

Objective: Our aim was to estimate whether diabetes mellitus (DM) may be associated with an increased risk of colorectal cancer (CRC) mortality in Japan. **Methods:** The Japan Collaborative Cohort (JACC) Study is a nationwide prospective study, initiated in 1988, which involves 110,585 subjects (age range: from 40 to 79 years; 46,395 males and 64,190 females). Our present analysis population comprised 96,081 (40,510 men and 55,571 women) who provided details on DM history. The questionnaire also included age, sex, weight, height, family history of CRC, smoking, drinking and exercise habits, and education. Cox proportional-hazard regression was used to estimate the hazard ratio (HR). We used SPSS 21 software to analyze all data. **Results:** Among the participants with DM, we followed up for 71,174 person-years and 640. deaths from CRC were confirmed; and, among the non-diabetic participants, 785 CRC deaths were identified during 1,499,324 person-years. After adjusting for multivariate confounding factors, such as age, sex, body mass index (BMI), family history of colorectal cancer, smoking habit, drinking habit, physical activity (sports and walking) and education, DM was associated with an increased risk of CRC death (HR 1.4, 95% confidence interval [CI] 1.0-2.0). Diabetic women, but not diabetic men, experienced increased mortality from CRC (HR 1.7, 95% CI 1.0-3.0). **Conclusion:** The risk of CRC mortality is significantly increased in both sexes and women with diabetes, but no significant increase was seen for diabetic men among Japanese.

Keywords: Cohort study- diabetes mellitus- colorectal cancer mortality- Japan Collaborative Cohort Study.

Introduction

Diabetes mellitus (DM) is widely considered as defects in glucose homeostasis and proper insulin function. The mechanism of how DM influences carcinogenesis is complicated and there are still many unclear details. However more and more experimental and observational study results have proved that biological mechanisms such as insulin resistance, hyperinsulinemia, insulin-like growth factor 1 (IGF-1), hyperglycemia, and chronic inflammation may induce carcinogenic effects. Specifically, hyperinsulinemia and elevated circulating IGF-1 concentrations have been confirmed to increase the CRC risk (Kaaks et al., 2000; Nakae et al., 2001; Ma et al., 2004; Wei et al., 2005; Zhang et al., 2013; Sen et al., 2014).

By as early as 1910, Maynard (1910) reported the correlations between DM and cancer risk. In Japan, Sasazuki (2013) conducted a pooled analysis from eight cohort studies (the total number of subjects was over 330,000) and estimated a summary hazard ratio (HR) for total and site-specific cancer. As one of the results, it was observed that DM statistically increased the risk of colon cancer (CC) incidence (HR 1.40).

Incidence and mortality are two important concepts. In general, it is possible that incidence and mortality have some overlapping risk factors, and that mortality may reflect the incidence to some extent. On the other hand, mortality is directly related to the prognosis of disease. The prognosis of CRC is deeply associated with CRC stage and treatments. In order to reduce CRC death, especially among diabetic patients, the current epidemiological status of CRC mortality should be paid more attention. Recently, many epidemiologic studies have proved to have a relationship between DM and CRC mortality (Weiderpass et al., 1997; Will et al., 1998; Hu et al., 1999; Coughlin et al., 2001; Jee et al., 2005; Ansary-Moghaddam et al., 2007; Tseng, 2012). However, there are almost no reports about the relationship between DM and CRC mortality in Japan.

*[1]Department of Public Health, Sapporo Medical University School of Medicine, [2]Sapporo Shirakabadai Hospital, [8]Department of Public Health, Hokkaido University Graduate School of Medicine, Sapporo, [3]Department of Preventive Medicine, Nagoya University Graduate School of Medicine, [4]Department of Public Health, Nagoya City University Graduate School of Medical Sciences, Nagoya, [5]Department of Public Health, Fujita Health University School of Health Sciences, [6]Department of Hygiene, Fujita Health University School of Medicine, Toyoake, Aichi, [7]Department of Epidemiology for Community Health and Medicine, Kyoto Prefectural University of Medicine Graduate School of Medical Science, Kyoto, Japan. *For correspondence: tance74@sapmed.ac.jp*

Furthermore, age, being overweight, lack of physical exercise, dietary habit, alcohol drinking, and smoking habit are known as common risk factors for CRC (Wakai et al., 2003; Tamakoshi et al., 2004; Wakai et al., 2005; Jacobs et al., 2007; Lee et al., 2007; Botteri et al., 2008; Okabayashi et al., 2012). In order to identify the real impact of DM for CRC death, all these recognized confounding factors should be adjusted, but it is not easy to achieve, in fact, because of missing data. Selecting inadequate confounding factors may lead to an increase or decrease in CRC risk among DM. Therefore, perhaps for this reason, there have been various conclusions in previous studies.

In this study, we prospectively analyzed the HR using JACC study data, by adjusting for multivariate such as age, sex, Body Mass Index (BMI), physical activity, family history of CRC, smoking habit, drinking habit, and education.

Material and Methods

JACC Study

The JACC Study was a nationwide multicenter collaborative study to prospectively estimate the risk influence of living habits on human health (Tamakoshi et al., 2013). The JACC study was initiated in 1988, over a total of 45 areas, and involved 110,585 study subjects (age range: from 40 to 79 years; including 46,395 male and 64,190 female participants). In 35 areas, a follow-up was completed at the end of 2009; but in four areas, it was stopped at the end of 1999, another four areas at the end of 2003, and in two areas, a follow-up was performed at the end of 2008. Data on deaths from major causes such as stomach cancer, lung cancer, CRC and cardiovascular diseases enabled examination of risk factors (Tamakoshi et al., 2013).

Data collection

We extracted 96,081 participants (40,510 men and 55,571 women) from the 110,585 participants of the JACC study. Our inclusion criterion is participants who answered whether they have a diabetic history. The participants were required to complete a self-administered questionnaire including age, gender, current weight and height, family history of CRC, smoking habit, drinking habit, exercise habit (sports and walking) and length of education.

Follow-up

We obtained the prior approval from the Director-General of the Prime Minister's Office and/or the Ministry of Health, Labor and Welfare, Japan, and confirmed and documented the death dates and death causes once a year or once every half year. It was considered as a study withdrawal when the study subjects moved away from the study area. We also recorded the withdrawal date once a year or once every half year.

Identification of CRC death cases

According to the tenth revision of the International Classification of Diseases (ICD-10), we defined participants whose direct cause of death was C18 as CC death, and C19 and C20 as rectum cancer (RC) death.

Statistical analysis

We used "person-years" to substitute the duration of follow-up, the person-years of all participants were accumulated. Moreover, we calculated the mortality rate of CRC for the diabetic participants and the non-diabetic participants. We also used HR and 95% confidence interval (CI) to evaluate the CRC mortality risk. Statistical significance was defined as $p<0.05$. A statistical analysis was performed by the Cox proportional hazard model, and we confirmed proportionality assumption for the Cox regression using log-log graphs in the Cox regression model. We adjusted for age, initially; in a subsequent multivariate analysis, we adjusted for smoking status (we used "smoking index" to evaluate smoking status, smoking index=number of cigarettes smoked per day×number of years smoked), alcohol consumption (current, former, never), length of education (attended school until 18 years old or not), family history of CRC (yes or no), BMI (BMI=weight in kilograms / [height in meters]^2, BMI $\geq$25 kg/m^2, 25>BMI$\geq$18.5kg/m^2, BMI<18.5 kg/m^2), and exercise (sports and walking) were further adjusted. We classified the frequency of sports (>5 hours/week, 3-4 hours/week, 1-2 hours/week, almost never) and walking (>1 hour/day, 0.5-1 hour/day, about 0.5 hour/day, almost never) according to sports and walking time.

We used the SPSS statistical software, version 21 to perform all the analyses.

This study was approved by the Ethics Committees of Hokkaido University Graduate School of Medicine and Sapporo Medical University.

Results

The baseline characteristics of our study are presented in Table 1. The prevalence of diabetes at baseline is 7.1 % among men, and 4.3 % among women. Diabetic participants were older, had a lower percentage of alcohol drinking, and had higher proportions of obesity among both men and women. However, the men with DM were better educated than the women.

During 71,174 person-years of follow-up among the participants with DM, 64 deaths from CRC were identified. Furthermore among the non-diabetic participants, 785 CRC deaths were identified during the follow-up of 1,499,324 person-years. After adjusting for multivariate confounding factors of CRC, DM was associated with increasing the risk of CRC mortality (HR 1.4, 95% CI 1.0 -2.0). Diabetic women experienced significant increase in risk of CRC mortality (HR 1.7, 95% CI 1.0-3.0), but among diabetic men no significant increase was found (HR 1.3, 95% CI 0.8 - 2.0) (Table 2). The interaction of gender and diabetes was not found, P=0.11.

Sub-site analyses were also performed. After multivariable adjustment was conducted for the same confounding factors, we observed that DM significantly increased CC mortality risk (HR 1.53, 95% CI 1.01-2.32;

Table 1. Characteristics of Subjects for History of Diabetes Mellitus

	Male			Female		
	History of diabetes mellitus			History of diabetes mellitus		
	yes	no	p value	yes	no	p value
Number of subjects	2,879	37,631		2,404	53,167	
Age, years; mean (standard deviation)	60.6 (9.1)	56.7 (10.2)	<0.01	63.2 (9.0)	57.0 (10.1)	<0.01
Smoking index						
mean (standard deviation)	561.1 (467.6)	498.1 (432.4)	<0.01	35.7 (114.9)	19.5 (105.7)	<0.01
Drinking habit (%)						
Current	70.6	75.8	<0.01	18.4	24.3	<0.01
Former	12.2	5.3		3.8	1.4	
Never	17.2	18.8		77.8	74.3	
Education (Attended school until) (%)						
>18 years	21.1	17.2	<0.01	8.4	10	<0.01
≤18 years	78.9	82.8		91.6	90	
Family history of colorectal cancer (%)						
Yes	1.6	1.8	0.32	2	2.2	0.41
No	98.4	98.2		98	97.8	
Body mass index (%)						
BMI<18.5 kg/m2	5.5	5.1	<0.01	5.4	5.9	<0.01
25>BMI≥18.5kg/m2	72.2	75.5		64.3	70.7	
BMI≥25 kg/m2	22.3	19.4		30.3	23.4	
Sports (%)						
>5 hours/week	8.6	7.1	<0.01	6.4	4.5	<0.01
3-4 hours/week	8.5	7.1		6.8	5.3	
1-2 hours/week	18.5	16.9		14.6	13.7	
Almost never	64.4	68.9		72.2	76.5	
Walking (%)						
>1 hour/day	41.5	49.8	<0.01	40.7	51.6	<0.01
0.5-1 hour/day	20.5	19.5		22.9	20.3	
About 0.5 hour/day	23.8	18.3		23.9	17.1	
Almost never	14.3	12.4		12.4	11.1	

P value for interaction of gender and diabetes 0.24), but did not significantly increase the RC mortality risk (HR 1.27, 95% CI 0.69-2.37; P value for interaction of gender and diabetes 0.3) (Table 3).

Discussion

In the present study, we found that DM significantly increased the CRC death risk for both sexes and women with diabetes, but no significant increase was seen for diabetic men among the Japanese.

The positive association between DM and CRC is supposed to be due to the pathophysiology of DM. Increasing evidence has proved the mechanisms such as insulin resistance, hyperinsulinemia and increased in bioavailable IGF-1 stimulate tumor growth (Kaaks et al., 2000; Nakae et al., 2001; Wei et al., 2005; Zhang et al., 2013; Sen et al., 2014).

Insulin resistance is described as a low response in the musculus skeleti and the hepar to the insulin action. To compensate for the resistance to insulin, pancreatic beta cell function increases and leads to hyperinsulinemia. However, when the compensatory secretion ability of pancreatic beta cell cannot catch up with the increasing requirements of insulin, hyperglycemia will appear, and eventually develop into type 2 DM. It has been reported that hyperinsulinemia and hyperglycemia can simulate tumor cell division and metastasis (Kaaks et al., 2000; Nakae et al., 2001; Ma et al., 2004; Richardson and Pollack, 2005; Wei et al., 2005).

On the other hand, increases in insulin levels can lead to reduction in the IGF-1 binding proteins (IGFBPs) synthesis, thus improving the bioactivity of IGF-1 (Renehan et al, 2006). Most circulating IGF-1 is in an inactive form in the serum due to binding to one of the IGFBPs. IGFBP-3 makes up almost 80% of the proportion of all IGF bindings. The majority view was that IGF-1 level is positively and IGFBP-3 level is negatively related

to CRC (Ma et al., 1999; Giovannucci et al., 2000), although we also noticed that inconsistent experiment results were reported in Japan recently (Suzuki et al., 2009).

Insulin binds with insulin receptors and IGF-1 binds with IGF-1 receptors respectively, and as a result, cell division is stimulated and apoptosis is inhibited, and there are a lot of evidences which can explain that insulin and IGF-1 play an important role in carcinogenesis (Kaaks et al., 2000; Nakae et al., 2001; Ma et al., 2004; Wei et al., 2005; Zhang et al., 2013; Sen et al., 2014).

Furthermore, the prognosis of CRC for diabetic patients absolutely cannot be ignored. Diabetic patients have a higher risk of postoperative complications than those without diabetes, such as postoperative infection and incision healing delay. Diabetic patients have a higher risk of cardiovascular death in the perioperative period (Juul et al., 2004); during the period of chemotherapy, steroids and some chemotherapy drugs may result in the worsening of diabetes.

The higher risk of CRC incidence, the poorer prognosis (van de Poll-Franse LV et al., 2007; Huang et al., 2011), and all these reasons may lead to an increased risk of CRC mortality for diabetic patients.

Interestingly, we found that DM significantly increased the risk of CRC mortality for women (HR 1.7, 95% CI 1.0-3.0), but no significant increase was seen for diabetic men (HR 1.3, 95% CI 0.8-1.9). It is possible that this gender difference has not been recognized. However the mechanism how sex hormone levels changed in diabetic patients had been elucidated, and changed sex hormone levels probably influence the risk of CRC mortality. Increased insulin resistance, hyperinsulinemia and hyperglycemia have been proven to inhibit the hepatic synthesis of sex hormone binding globulin (SHBG), and SHBG has a high specific affinity for testosterone and oestradiol (Pugeat et al., 1991; Haffner, 1996). In diabetic women, decreased SHBG led to increased levels of bioavailable testosterone. On the contrary, in diabetic men, decreased SHBG can also increase the bioavailable testosterone to some degree; but in fact, testosterone concentration of diabetic men is lower than no-diabetic men, because gonadotropic stimulation significantly decreases in diabetic men, thus the testosterone production in the testicles reduced greatly (Dhindsa et al., 2004; Dandona and Dhindsa, 2011). Recently, it has been proven that testosterone increases colonic adenomas (Amos-Landgraf et al., 2014). Of course, these can only explain that changed sex hormone levels may alter the risk of CRC incidence and lead to gender differences, but we do not have enough evidence to prove whether there is a gender bias in the treatments of CRC among diabetic patients.

The main results of our study for DM and CRC mortality were consistent with most of the previous studies (Weiderpass et al., 1997; Hu et al., 1999; Coughlin et al., 2001; Jee et al., 2005; Tseng, 2012). Especially Jee (2005) and Tseng (2012), all their study subjects were East Asians (Taiwanese, Korean, respectively), just like our study, and they reported similar conclusions, which

Table 2. Hazard Ratio (HR) and its 95% Confidence Interval (95% CI) of Risk of Colorectal Cancer Death

History of diabetes mellitus	Male					Female				All						
	No. of deaths	age-adjusted HR (95% CI)	p value	multivariable-adjusted HR (95% CI)†	p value	No. of deaths	age-adjusted HR (95% CI)	p value	multivariable-adjusted HR (95% CI)†	No. of deaths	Person-years	Mortality rate	age,sex-adjusted HR (95% CI)	p value	multivariable-adjusted HR (95% CI)‡	p value
no	420	1.0		1.0		365	1.0		1.0	785	1,499,324	52.4/105	1.0		1.0	
yes	35	1.1 (0.8~1.6)	0.6	1.3 (0.8~1.99)	0.28	29	1.6 (1.1~2.4)	0.01	1.7 (1.0~3.0) 0.05	64	71,174	89.9/105	1.3 (1.0~1.7)	0.04	1.4 (1.0~2.0)	0.04

†Adjusted for age, BMI, family history of colorectal cancer, smoking habit, drinking habit, sports, walking, and education; CI, confidence interval; HR, hazard ratio ‡Adjusted for age, sex, BMI, family history of coloreccancer, smoking habit, drinking habit, sports, walking, and education.

Table 3. Hazard Ratio (HR) and its 95% Confidence Interval (95% CI) of Risk of Colon and Rectal Cancer Death

colon cancer death

History of diabetes mellitus	Male						Female						All								
	No. of deaths	age-adjusted HR	(95% CI)	p value	multivariable-adjusted † HR	p value	No. of deaths	age-adjusted HR	(95% CI)	p value	multivariable-adjusted † HR	p value	No. of deaths	Person-years	Mortality rate	age, sex-adjusted HR	(95% CI)	p value	multivariable-adjusted ‡ HR	(95% CI)	p value
no	235	1.00	(95% CI)		1.0	(95% CI)	260	1.00	(95% CI)		1.0	(95% CI)	495	1,499,324	33.0/105	1.0	(95% CI)		1.0	(95% CI)	
yes	23	1.29	(0.84~1.98)	0.25	1.5	(0.9~2.5) 0.16	22	1.69	(1.1~2.6)	0.12	1.6	(0.8~3.1) 0.15	45	71,174	63.2/105	1.4	(1.1~1.9)	0.01	1.5	(1.0~2.3)	0.05

rectal cancer death

History of diabetes mellitus	Male						Female						All								
	No. of deaths	age-adjusted HR	(95% CI)	p value	multivariable-adjusted † HR	p value	No. of deaths	age-adjusted HR	(95% CI)	p value	multivariable-adjusted † HR	p value	No. of deaths	Person-years	Mortality rate	age, sex-adjusted HR	(95% CI)	p value	multivariable-adjusted ‡ HR	(95% CI)	p value
no	185	1.00	(95% CI)		1.0	(95% CI)	105	1.00	(95% CI)		1.0	(95% CI)	290	1,499,324	19.3/105	1.0	(95% CI)		1.0	(95% CI)	
yes	12	0.88	(0.49~1.58)	0.67	0.9	(0.5~2.1) 0.98	7	1.55	(0.7~3.3)	0.27	2.1	(0.8~6.0) 0.15	19	71,174	26.7/105	1.0	(0.7~1.7)	0.83	1.3	(0.7~2.4)	0.44

†Adjusted for age, BMI, family history of colorectal cancer, smoking habit, drinking habit, sports, walking, and education; ‡Adjusted for age, sex, BMI, family history of coloreccancer, smoking habit, drinking habit, sports, walking, and education; CI, confidence interval; HR, hazard ratio

was that DM significantly increases the risk of colorectal cancer mortality.

We also calculated the HR (95 % CI) of CRC incidence (adjusted for the same multivariate confounding factors). For diabetic men and women combined, the HR value was 1.3 (0.9-1.8); for diabetic men, the HR value was 1.2 (0.8-1.8); for diabetic women, the HR was 1.3 (0.8-2.1). These results only showed an increase in trend of CRC incidence risk for diabetic patients, but did not link to CRC mortality completely.

Detection bias must be noted. Generally speaking, diabetic patients are inclined to receive medical service; therefore, they may have more opportunities to undergo cancer screening tests. From the above, we can infer that diabetic participants have a higher detection rate of early CRC than non-diabetic participants. Certainly, because early detection and early treatment might improve the prognosis of CRC, the mortality of CRC might also be influenced.

The strengths of our study included a prospective design which avoided exposure recall bias; moreover the JACC study is one of the largest cohort studies in Japan. The study participants' characteristics were similar to the Japanese general population (Tamakoshi et al., 2013). Thus we can consider that the results of the JACC study may be used as a representative of the Japanese. We adequately adjusted for almost all common confounding factors, which may have contributed to proving the relationship between DM and CRC death more clearly and definitely.

The potential limitations of our study should not be ignored. First, we assessed the DM history of the participants based on participants' self-reports, which might lead to classification error. Second, we did not differentiate the type of DM, although the vast majority of adult diabetics in Japan are generally regarded as type 2. Third, we did not adjust the influence of multiple drug therapies in diabetic patients, although some drugs may affect the incidence of CRC (Li, 2011). Something similar is that we did not adjust for insulin therapy, although at present, it is controversial whether or not exogenous insulin injection increases cancer risk (Tseng, 2012; Home, 2013; Yin et al., 2014). Fourth, previous studies have shown that the influence of DM for CRC was largest in the first 15 years after DM was diagnosed (Hu et al., 1999; Flood et al., 2010), but we did not evaluate the duration of DM. Fifth, among diabetic men, no significant increase of CRC risk was found (HR 1.3, 95% CI 0.82-1.99). However, if we got increased sample size and power more than this cohort study (about 96,000 subjects), it would be possible to exceed significance level (Breslow and Day, 1987).

Our study demonstrated that DM significantly increased the risk of CRC mortality for both sexes and women with diabetes, but no significant increase was seen for diabetic men among the Japanese.

Acknowledgments

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