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ORIGINAL ARTICLE

Prospective study of cancer in Japanese patients with type 2 diabetes: the Fukuoka Diabetes Registry

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Abstract

Background Although the association between type 2 diabetes and cancer has been reported, few epidemiological studies have been conducted in Japanese patients whose leading cause of death is cancer. We prospectively studied the incidence of site-specific cancer, risk factors for developing cancer, cancer death, and survival in Japanese patients with type 2 diabetes.

Methods We followed 4923 participants (mean age, 65 years) with type 2 diabetes attending an outpatient diabetes clinic for a median of 5.3 years (follow-up rate, 99.0%).

Results During the follow-up period, cancer occurred in 450 participants (incidence rate, 22.3/1000 person-years in men and 12.2/1000 person-years in women). In men, prostate cancer was the most common cancer (4.3/1000 person-years), colorectal cancer was the second (3.6/1000 person-years), and gastric cancer was the third (3.3/1000 person-years). In women, colorectal cancer was the most common cancer (2.6/1000 person-years), gastric cancer was the second (2.0/1000 person-years), and breast cancer was the third (1.4/1000 person-years). Smoking, male sex, low-density lipoprotein cholesterol, family history of cancer, and reduced intake of isoflavone daidzein were significant risk factors for developing cancer using multivariable Cox proportional hazards models. The leading cancer death was lung cancer in men and pancreatic cancer in women. The survival was the best for prostate cancer and the worst for pancreatic cancer (2-year cancer-specific survival 95.4%, 30.0%, respectively).

Conclusions Since the leading cause of death in patients with type 2 diabetes is cancer in Japan, clinicians should be aware of epidemiological data regarding cancer besides diabetic complications.

Keywords Cancer · Cohort study · Isoflavone · Type 2 diabetes

Introduction

The association between type 2 diabetes and cancer has been consistently reported [1–6]. Some evidence suggests that cancer risk associated with diabetes is higher in Asians than in non-Asians [7]. According to the Committee on Causes of Death in Diabetes Mellitus in the Japan Diabetes Society [8], cancer has been the leading cause of death in patients with diabetes since 1991–2000 (cancer 38%, infection 17%, and vascular disease 15% during 2001–2010), and pooled analysis of eight cohort studies in the Japanese general population showed that diabetes was associated with a 20% increased risk of developing any cancer [9]. Although the mechanisms may include enhanced signaling of insulin-like growth factor-1, increased oxidative stress, inflammation and production of advanced glycation end glycation [7], risk factors for patients with type 2 diabetes developing cancer remain to be fully understood [10, 11].

Since site-specific incidence of cancer varies with aging, the knowledge of site-specific incidence in diabetic patients of varying age is important in clinical management. Furthermore, the prognosis of cancer has not been reported in Japanese patients with type 2 diabetes to our knowledge. In this context, we prospectively studied the incidence of

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site-specific cancer, risk factors for developing cancer, cancer death, and survival rate in Japanese patients with type 2 diabetes.

Methods

Participants

The Fukuoka Diabetes Registry includes 5131 out-patients who were regularly followed in 16 diabetes specialist clinics in Fukuoka Prefecture, Japan (UMIN Clinical Trial Registry 000002627) [12]. The participants were registered between April 2008 and October 2010. Exclusion criteria were: (1) patients aged less than 20 years; (2) those with drug-induced diabetes; (3) those with end-stage renal disease requiring dialysis; (4) those with serious diseases other than diabetes mellitus, such as cancer. After excluding 208 participants with type 1 diabetes, the remaining 4923 participants were enrolled in the current study. The study was approved by the Kyushu University Institutional Review Board (approval number 290-01, date of approval 4 Jan 2008), and followed the ethics of the Helsinki declaration with written informed consent.

Baseline evaluation

Diabetes duration and family history of cancer (parents, siblings, and children) were checked at the baseline. Smoking habits and alcohol consumption were classified as either current user or not. Information regarding medications was collected. Leisure-time physical activity (LTPA) was assessed as metabolic equivalent hours per week (MET·h/w) using Ainsworth's methods [13]. HbA_{1c} was determined by high-performance liquid chromatography (Tosoh Corp., Tokyo, Japan), and serum low-density lipoprotein cholesterol (LDL-C) by enzymatic methods. A dietary survey was performed using a self-administered brief type diet history questionnaire (BDHQ; Gender Medical Research Inc., Tokyo, Japan) regarding the frequency of 58 food items. The validity of ranking the energy-adjusted intake of nutrients including fiber and daidzein intake was reported in an adult Japanese population [14].

Investigation on the occurrence of cancer

History of cancer was checked at the baseline, and participants under treatment were excluded. The development of cancer was annually assessed by a self-administered questionnaire and/or reviewing medical records during the follow-up period. Diagnosis of cancer was confirmed by participants' attending specialists. The follow-up period was the time from enrollment to the first cancer diagnosis, death, or the planned study ending, whichever occurred first. The cause of death was determined based on the International Statistical Classification of Diseases and Related Health Problems (ICD-10).

Statistical analysis

Student's *t* tests and Chi-square tests were used for continuous and categorical variables, as appropriate. Multivariable Cox proportional hazards models were used to evaluate risks for developing cancer. The variables included age, sex (dichotomous), duration of diabetes, family history of cancer (dichotomous), current smoking (dichotomous), current drinking (dichotomous), LTPA, HbA_{1c}, and insulin therapy (dichotomous). Daily daidzein intake was adjusted for using quartiles (quartile one <4.5 g/1000 kcal, quartile two 4.5–7.6 g/1000 kcal, quartile three 7.6–11.8 g/1000 kcal, quartile four ≥ 11.8 g/1000 kcal), and LDL-C was adjusted for three categories (<100 mg/dl, 100–120 mg/dl, ≥ 120 mg/dl). The age and sex matched case–control study was performed between participants with cancer and without using nearest available matching. The results are expressed as hazard ratio (HR) with 95% confidence intervals (95% CI). Statistical analyses were conducted using JMP software (ver. 12; SAS Institute Inc., Cary, NC, USA), and $p<0.05$ was considered to be statistically significant.

Results

Baseline characteristics

Cancer developed in 450 participants (317 men and 133 women) during the follow-up period (median follow-up period, 5.3 years; follow-up rate, 99.0%). Baseline characteristics of the participants are shown in Table 1. In men, participants who developed cancer were older, had lower BMI, a longer duration of diabetes, a higher prevalence of cancer family history and smoking, lower HbA_{1c} and LDL-C, and a lower prevalence of biguanide users than those who did not develop cancer. In women, participants who developed cancer were older, had higher BMI, a lower daily intake of daidzein, and a lower prevalence of pioglitazone users than those who did not develop cancer. The prevalence of previous cancer did not differ in those who developed cancer and those who did not for either sex. Stomach cancer was the leading cancer type in men, and breast cancer was the leading cancer type in women.

Incidence of site-specific cancer

Table 2 shows the number and incidence of the top 10 site-specific cancer types. There were 474 cases of cancer

Table 1 Clinical characteristics of participants with type 2 diabetes

	Men		Women	
	New cancer (−)	New cancer (+)	New cancer (−)	New cancer (+)
n	2441	317	1985	133
Age (years)	64.6 ± 10.2	69.5 ± 7.3***	65.8 ± 10.4	69.2 ± 8.4***
BMI (kg/m^2)	23.6 ± 3.3	23.0 ± 2.9**	23.9 ± 4.3	24.9 ± 4.9*
Duration of diabetes (years)	16.3 ± 10.9	18.2 ± 11.2**	14.3 ± 9.8	15.2 ± 9.5
Family history of cancer	955 (39.1%)	151 (47.6%)**	871 (43.9%)	60 (45.1%)
Past history of cancer	239 (9.8%)	31 (9.8%)	180 (9.1%)	7 (5.3%)
Stomach	71	9	20	0
Colon/rectum	68	9	19	0
Lung	14	2	7	0
Liver	14	1	3	1
Prostate	38	5	–	–
Breast	–	–	62	3
Uterus	–	–	46	3
Others	59	6	35	0
Current smoking	648 (26.5%)	104 (32.8%)*	133 (6.7%)	9 (6.8%)
Current drinking	1379 (56.5%)	181 (57.1%)	333 (16.8%)	17 (12.8%)
LTPA (MET h/week)	13.6 ± 16.2	14.8 ± 17.4	9.1 ± 12.6	9.2 ± 11.1
Daily fiber intake (mg/1000 kcal)	7.04 ± 2.08	7.09 ± 2.13	8.29 ± 2.17	8.33 ± 2.12
Daily daidzein intake (mg/1000 kcal)	8.43 ± 5.45	8.11 ± 5.02	8.99 ± 5.17	7.46 ± 4.61***
HbA_{1c} (%)	7.36 ± 1.02	7.23 ± 0.90*	7.55 ± 1.08	7.54 ± 1.05
LDL-C (mg/dl)	108 ± 27	103 ± 25**	114 ± 27	110 ± 22
Statin use	875 (35.8%)	105 (33.1%)	1056 (53.2%)	81 (60.9%)
Biguanide use	728 (29.8%)	75 (23.7%)*	760 (38.3%)	56 (42.1%)
Pioglitazone use	325 (13.3%)	35 (11.0%)	261 (13.1%)	9 (6.8%)*
Insulin use	655 (26.8%)	95 (30.0%)	602 (30.3%)	46 (34.6%)

Data are expressed as number of participants or mean ± SD

BMI body mass index, *LTPA* leisure-time physical activity, *HbA_{1c}* glycated hemoglobin, *LDL-C* low-density lipoprotein cholesterol

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. those without new cancer

including double cancer in 20 (15 males and 5 females) and triple cancer in two. In men, prostate cancer was the most common cancer (4.3/1000 person-years), colorectal cancer was the second (3.6/1000 person-years), and gastric cancer was the third (3.3/1000 person-years). In women, colorectal cancer was the most common cancer (2.6/1000 person-years), gastric cancer was the second (2.0/1000 person-years), and breast cancer was the third (1.4/1000 person-years).

Incidence of cancer according to age

The incidence of cancer according to three age categories is shown in Fig. 1. As shown in Fig. 1a, the incidence of cancer at any site was consistently higher in men than in women and the difference became greater with aging. In men (Fig. 1b), prostate cancer increased rapidly with aging and the incidence was the highest after 65 years. Colorectal and pancreatic cancer increased with aging. On the other hand, lung and liver cancer remained almost stable from 65–75 to ≥ 75 years, while gastric cancer decreased from 65–75 to ≥ 75 years. In women (Fig. 1c), the incidence of colorectal cancer was the highest in < 65 years and ≥ 75 years and that of gastric cancer was the highest between 65 and 75 years. Lung and pancreatic cancer increased with aging, whereas the incidence of breast and liver cancer was almost stable, and gastric cancer decreased from 65–75 to ≥ 75 years.

Risk factors for developing cancer

Risk factors for developing cancer were investigated in those who developed cancer after 1 year of the registration and who had no past history of cancer, using a multi-adjusted Cox proportional model (Table 3). Multivariate adjustments included age, sex, duration of diabetes, family history of cancer, BMI, current smoking, current drinking, LTPA, daily daidzein intake, HbA_{1c}, LDL-C, and insulin therapy. Cancer developed more frequently in current

Table 2 Number and incidence of top ten cancer types in men and women with type 2 diabetes

	Men ($n=2790$)	
	Number	Incidence (/1000 person-years)
Participants	317	23.3
Site-specific		
Prostate	61	4.3
Colon/rectum	51	3.6
Stomach	46	3.3
Lung	38	2.7
Liver	29	2.1
Bladder	21	1.5
Pancreas	16	1.1
Hematopoietic system	16	1.1
Kidney/urinary tract	13	0.9
Esophagus	9	0.6
	Women ($n=2133$)	
	Number	Incidence (/1000 person-years)
Participants	133	12.2
Site-specific		
Colon/rectum	29	2.6
Stomach	22	2.0
Lung	15	1.4
Breast	16	1.4
Uterus	8	0.7
Hematopoietic system	7	0.6
Thyroid	7	0.6
Liver	5	0.5
Pancreas	6	0.5
Kidney/urinary tract	4	0.4

smokers than nonsmokers (HR 1.66, 95% CI 1.27–2.16), in men than women (HR 1.65, 95% CI 1.28–2.14), in those with < 100 mg/dl LDL-C than those with ≥ 120 mg/dl LDL-C (HR 1.43, 95% CI 1.09–1.88), and in those with a family history of cancer than those without (HR 1.28, 95% CI 1.03–1.58). On the other hand, increased daily intake of daidzein isoflavone was significantly associated with lower incidence of cancer (Q4 vs. Q1, HR 0.67, 95% CI 0.50–0.90). However, BMI (obesity), alcohol consumption, LTPA, HbA_{1c}, metformin use, pioglitazone use, insulin therapy, or statin use was not associated with the occurrence of cancer. In addition, as patients with cancer were statistically older than those without, age and sex matched case–control study was performed (1:1 matching, $n=343$). Cancer developed more frequently in current smokers than nonsmokers (HR 1.65, 95% CI 1.28–2.10), and increased daily intake of daidzein isoflavone was significantly associated with lower incidence of cancer (Q2 vs. Q1, HR 0.73, 95% CI 0.55–0.97; Q3 vs. Q1, HR 0.60, 95% CI 0.44–0.81; Q4 vs. Q1, HR 0.67, 95% CI 0.49–0.89). However, LDL-C or family history of cancer was not a significant risk factor for cancer development.

Cancer death and survival of those with major cancer types

During the follow-up period, 114 participants (83 men and 31 women) died of cancer. Lung cancer was the leading cause of cancer death ($n=19$), liver was the second ($n=13$), and pancreatic was the third ($n=10$) in men. In women, pancreatic cancer was the leading cause of cancer death ($n=5$). Figure 2 depicts survival after the diagnosis of cancer in the prostate, colon/rectum, stomach, liver, lung, and pancreas. Two-year cancer-specific survival was 95.4% for prostate cancer, 89.1% for colorectal cancer, 85.0% for stomach cancer, 79.4% for liver cancer, 57.9% for lung cancer, and 30.0% for pancreatic cancer.

Discussion

The incidence of site-specific cancer varies according to age, ethnicity, and country of origin in men and women. The incidence and prognosis of site-specific cancer in Japan has been estimated by the Monitoring of Cancer Incidence in Japan (MCIJ) project [15]. Regarding estimated cancer incidence in 2017, stomach was the most common cancer site (16%) for men, followed by lung (15%), prostate (15%), colon/rectum (15%), and liver (5%). The most common cancer site for women was breast (20%), followed by colon/rectum (15%), stomach (10%), lung (10%), and uterus (6%). Prostate cancer is the most frequently diagnosed cancer among men in developed countries [16], and in Japan its annual crude incidence markedly increased from 6.9/100,000 persons in 1980 to 126.6/100,000 persons in 2011 along with economic development and aging of the population [15]. The risk factors for prostate cancer include increased consumption of animal fat, obesity, and physical inactivity [17]. Prostate cancer was the leading cancer in those aged ≥ 65 years in our cohort, and its incidence was higher in our cohort than in the MCIJ project (Table 4; 5.9 vs. 4.1/1000 person-years in 65–75 years; 7.8 vs. 5.2/1000 person-years in ≥ 75 years). Diabetes is associated with a reduced risk of prostate cancer in studies conducted mostly in Western countries [18], whereas a meta-analysis in Asian countries showed that diabetes is associated with an increased risk of prostate cancer [19]. Moreover, incidence rates of prostate cancer vary by the differences in the use of prostate-specific antigen (PSA) testing [17], although the rate of PSA testing was not determined in the present study. In addition, the incidence of liver and pancreatic cancer was higher in our cohort than in the MCIJ project in men (Table 4; liver cancer, 2.6 vs. 1.1/1000

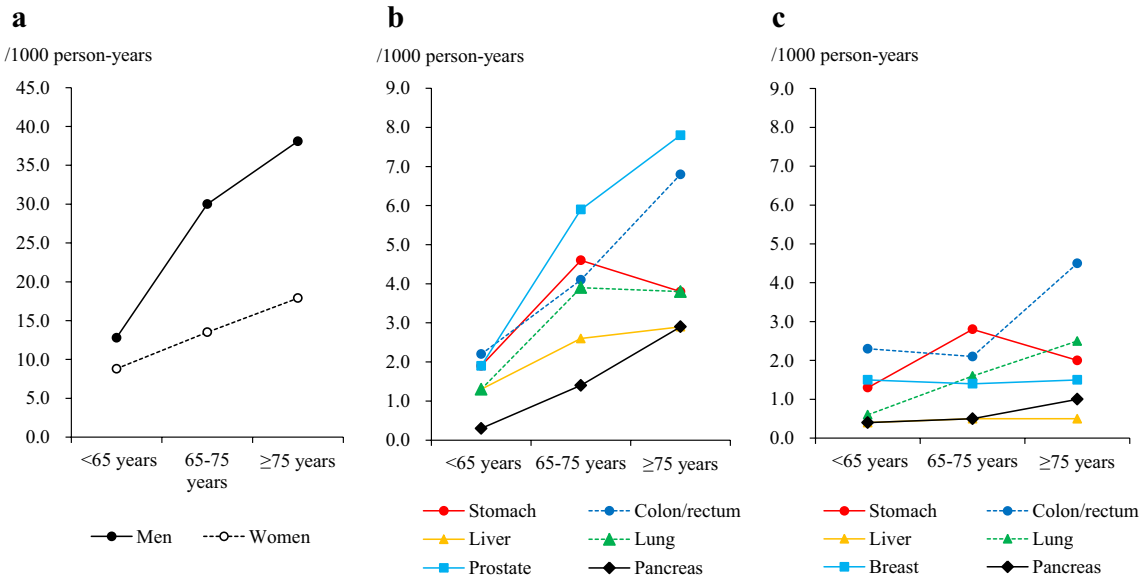

Fig. 1 **a** Incidence of cancer at any site in men (solid line) and women (dotted line) according to three age categories. **b** Incidence of site-specific cancer in men. **c** Incidence of site-specific cancer in women. Red line, stomach; blue line, colon/rectum; gold line, liver; green line, lung; light blue line, prostate; black line pancreas

Table 3 Significant risk factors for developing cancer after 1 year of enrollment in participants with type 2 diabetes without past history of cancer

	Incidence	HR	95% CI	*p*
Smoking				
−	14.3	Ref.		
+	21.3	1.66	1.27–2.16	< 0.001
Sex				
Women	11.1	Ref.		
Men	19.1	1.65	1.28–2.14	0.0001
LDL-C (mg/dl)				
≥ 120	11.2	Ref.		
100–120	17.2	1.45	1.10–1.92	< 0.01
< 100	18.6	1.43	1.09–1.88	< 0.01
Family history of cancer				
−	14.1	Ref.		
+	17.7	1.28	1.03–1.58	< 0.05
Daily daidzein intake (g/1000 kcal)				
Q1 (< 4.5)	19.7	Ref.		
Q2 (4.5–7.6)	15.5	0.82	0.62–1.09	ns
Q3 (7.6–11.8)	12.7	0.62	0.46–0.84	< 0.01
Q4 (≥ 11.8)	14.4	0.67	0.50–0.90	< 0.01

Multivariate adjustments included age, sex (dichotomous), duration of diabetes, family history of cancer (dichotomous), BMI, current smoking (dichotomous), current drinking (dichotomous), LTPA, daily daidzein intake (quartiles), HbA_{1c}, LDL-C (three categories), and insulin therapy (dichotomous)

LDL-C low-density lipoprotein cholesterol

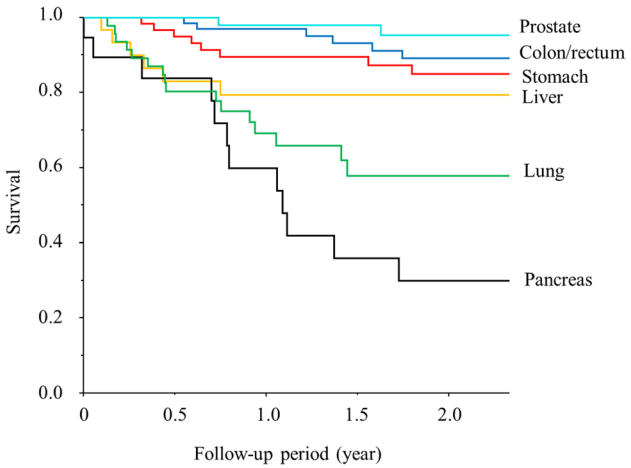

Fig. 2 Kaplan–Meier survival curves after diagnosis of cancer in the prostate (light blue line), colon/rectum (blue line), stomach (red line), liver (gold line), lung (green line) and pancreas (black line) in Japanese participants with type 2 diabetes

person-years in 65–75 years, 2.9 vs. 2.0/1000 person-years in ≥ 75 years; pancreatic cancer, 1.4 vs. 0.8/1000 person-years in 65–75 years, and 2.9 vs. 1.3/1000 person-years in ≥ 75 years). The pooled analysis of eight cohort studies in the Japanese general population showed that the incidence of liver and pancreatic cancer was significantly increased in those with diabetes as compared with those without (liver cancer, HR 2.07; pancreatic cancer, HR 1.58) [9]. In women aged 65–75 years, stomach cancer was the leading cancer in our cohort, and its incidence was higher in our cohort than

in MCIJ project (Table 4; 2.8 vs. 1.3/1000 person-years). In those aged ≥ 75 years, colorectal cancer was the leading cancer type in our cohort as well as in the MCIJ project, although its incidence was higher in our cohort than in the MCIJ project (Table 4; 4.5 vs. 3.2/1000 person-years).

The present study showed that risk factors for any cancer included well-known risks such as smoking, male sex, low LDL-C, and family history of cancer [20]. As sex differences in cancer incidence increased with advancing age, the older age of our cohort with mean of 65 years led to higher HR for men (HR 1.65) than the MCIJ project (HR 1.3). HR for current smokers (1.66) was similar to the previous report (HR 1.53) [21]. Low cholesterol has been reported to be associated with cancer [22, 23], although statin use is not a cancer risk [24]. In the age and sex matched case–control study (1:1 matching, $n = 343$), however, LDL-C or family history of cancer was not a significant risk factor for cancer development, although the number of study participants was small. Alcohol consumption [25] and physical inactivity [26] were significant risks for cancer in a large general population in Japan, whereas obesity was not because the degree of obesity is much lower in Japanese individuals than in Westerners [27, 28]. In the present study, alcohol consumption, physical activity, or obesity was not associated with cancer risks. The difference may be explained by the study population (general population vs. registry of diabetic patients) and the number of study participants. On the other hand, increased isoflavone daidzein intake was associated with a reduced risk of cancer in the current study. Isoflavone intake is high in the Japanese diet because of the high consumption of soybeans such as tofu. It has been reported that soy isoflavones, which are phytoestrogens, play a protective role in breast cancer [29], prostate cancer [30], colorectal cancer [31], and gastric cancer [32]. Regarding other nutrients or mineral, salt intake was associated with cancer risk [33]. However, salt intakes were not different between those with cancer development and without in either sex (male 6.0 ± 1.3 g/1000 kcal in those with cancer development, 6.0 ± 1.3 g/1000 kcal in those without cancer development; female 6.0 ± 1.2 g/1000 kcal in those with cancer development, 6.1 ± 1.3 g/1000 kcal in those without cancer development). This may be because salt-restricted diet is frequently advised to diabetic patients due to hypertension and cardiovascular disease.

Table 4 Cancer incidence in Fukuoka Diabetes Registry (FDR) and the Monitoring of Cancer Incidence in Japan project (MCIJ) [25]

	Cancer incidence (/1000 person-years)			Cancer incidence (/1000 person-years)	
	FDR	MCIJ		FDR	MCIJ
Men			Women		
Prostate			Stomach		
65–75 years	5.9	4.1	65–75 years	2.8	1.3
≥ 75 years	7.8	5.2	≥ 75 years	2.0	2.2
Liver			Colon		
65–75 years	2.6	1.1	65–75 years	2.1	2.2
≥ 75 years	2.9	2.0	≥ 75 years	4.5	3.2
Pancreas					
65–75 years	1.4	0.8			
≥ 75 years	2.9	1.3			

According to survival statistics of the Japanese Association of Clinical Cancer Centers [35], the 2-year survival rate of cancer diagnosed during 2007–2009 was 100% for prostate cancer ($n = 9151$), 86.5% for colorectal cancer ($n = 14{,}551$), 80.9% for stomach cancer ($n = 22{,}000$), 60.5% for liver cancer ($n = 4740$), 57.9% for lung cancer ($n = 19{,}997$), and 22.0% for pancreatic cancer ($n = 4489$). These figures are almost similar to our results: 95.4% for prostate cancer, 89.1% for colorectal cancer, 85.0% for stomach cancer, 79.4% for liver cancer, 57.9% for lung cancer, and 30.0% for pancreatic cancer. Although cancer patients with diabetes might receive less-aggressive cancer treatment because of the concomitant diabetic complications, it was reported that cancer-specific survival was not affected by preexisting diabetes in patients with prostate cancer [36] or colorectal cancer [37].

A strength of our study is the prospective cohort design with diabetes-related lifestyle and laboratory data with a high follow-up rate (99.0%). This study had some limitations. First, a self-administered questionnaire was used, which may have affected accurate reporting of the incidence of cancer. Therefore, we assessed its reliability in 649 participants using the medical records. There was no disagreement in the occurrence and non-occurrence of cancer between participants' medical records and the self-administered questionnaire. The second limitation was that participants regularly attended specialist diabetes clinics and may have routinely received cancer screening. Therefore, the incidence of cancer in the current study may not represent the national data in Japan. Third, the present study was not large enough to investigate the incidence and survival of site-specific cancer by sex and risk factors for developing

cancer in detail. We did not assess the staging of cancer or its treatment. Advanced cancer may lead to a poorer prognosis. Since the incidence of site-specific cancer is lower than that of diabetic complications, a larger and longer cohort study will be necessary to investigate specific risk factors and survival for site-specific cancer. However, there are few prospective studies regarding the incidence of site-specific cancer, risk factors for developing cancer, and survival in Japanese patients with type 2 diabetes.

The present prospective study demonstrated that: (1) the leading cancer was prostate cancer in men and colorectal cancer in women; (2) risk factors for developing cancer included smoking, male sex, low LDL-C, family history of cancer, and reduced intake of isoflavone daidzein; (3) the leading cancer death was lung cancer in men and pancreatic cancer in women; and (4) the survival was the best for prostate cancer and the worst for pancreatic cancer. Since the leading cause of death in patients with type 2 diabetes is cancer in Japan [8], clinicians should be aware of epidemiological data regarding cancer besides diabetic complications.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest associated with this manuscript.

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