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Impact of coexisting diabetes on survival and risk of developing second primary cancer in diabetes patients receiving drug therapy: A multicenter retrospective cohort study of patients with cancer in Japan

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ABSTRACT

Aims/Introduction: We investigated the association between coexisting diabetes at the time of cancer diagnosis, and the overall survival and incidence of second primary cancer in patients with cancer and receiving drug therapy for diabetes.

Materials and Methods: We used cancer registry and administrative data of patients diagnosed with cancer at designated cancer care hospitals in Osaka Prefecture between 2010 and 2015. The presence of diabetes was identified from the prescription records of antidiabetic drugs in Diagnosis Procedure Combination System data. After adjusting for patient characteristics, we compared overall survival between patients with cancer with coexisting diabetes and those without coexisting diabetes using the Cox proportional hazards model. In addition, the impact of coexisting diabetes on the risk of developing second primary cancer was evaluated using a competing risk analysis.

Results: Of the 131,701 patients with cancer included in the analysis, 6,135 (4.7%) had coexisting diabetes. The 5-year survival rates for patients with and without coexisting diabetes were 56.2% (95% confidence interval 54.8–57.6) and 72.7% (95% confidence interval 72.4–73.0), respectively. Coexisting diabetes was associated with a higher risk of developing second primary cancer (subdistribution hazard ratio 1.23; 95% confidence interval 1.08–1.41). In site-specific analysis, coexisting diabetes was associated with an increased risk for the development of second primary cancer of multiple myeloma, and cancer of the uterus, pancreas and liver.

Conclusions: Coexisting diabetes was associated with a higher mortality and risk of developing second primary cancer in Japanese patients with cancer and on drug therapy for diabetes.

INTRODUCTION

Diabetes is a major public health issue, and its global prevalence continues to increase[1]. The National Diabetes Statistics Report (2020)[2] states that 34.2 million people (10.5% of the USA population) have diabetes. According to the 2016 National Health and Nutrition Survey in Japan[3], approximately 10 million people (12.1% of the total adult population) have diabetes in Japan. Diabetes is a major comorbidity in patients with cancer[4], and the impact of coexisting diabetes on the prognosis of

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patients with cancer remains a topic of debate[5–11]. In a meta-analysis of 23 studies in which patients were diagnosed with cancer between 1970 and 2006, Barone *et al.* reported a 41% increase in mortality rate in patients with cancer with diabetes compared with those without diabetes[5]. In a register-based study that included all patients with cancer diagnosed in Denmark between 1995 and 2009, the mortality rate was higher in patients with diabetes than in those without diabetes (the hazard ratios [HRs] of insulin-treated patients compared with patients without diabetes were 1.49 and 1.46 for men and women, respectively)[7]. However, reports on the impact of diabetes on the prognosis of patients with cancer have not been fully updated with recent advancements in treatment and improved prognosis. Furthermore, many studies have been carried out on Western populations, whereas studies on Asian populations are sparse. Kodama *et al.* examined ethnic differences in the association between insulin sensitivity and insulin responses, and reported that East Asians have a limited innate capacity to secrete insulin and are at higher risk of developing diabetes due to β-cell depletion[12]. Given that the mechanism by which diabetes affects cancer is hypothesized to be the induction of cancer cell proliferation by high glucose and insulin levels[13], such ethnic differences might affect the prognostic impact of diabetes in patients with cancer. Therefore, it is worthwhile to examine the impact of coexisting diabetes on survival of patients with cancer in the Japanese population.

Second primary malignancies account for 18% of all cancers in the USA[14]. In Japan, the 10-year cumulative risk of developing second primary cancer in patients who develop primary cancer aged in their 60s is approximately 13%[15]. Thus, second primary cancer is not a rare condition, and the risk factors for developing second primary cancers are notable. Sung *et al.* carried out a retrospective study of 1.54 million individuals diagnosed with primary cancer in the USA between 1992 and 2011, and reported that obesity and smoking were associated with the development of second primary cancer in some cancer sites[16]. However, they did not report an association between diabetes and second primary cancer. Only a few reports have examined the association between diabetes and the risk of developing second primary cancer. A retrospective analysis of patients with colorectal cancer in the Czech Republic[17] and of patients with postoperative gastric cancer in Japan[18] showed that the coexistence of diabetes increased the risk of developing second primary cancer. However, to the best of our knowledge, no study to date has investigated the effects of diabetes on the development of second primary cancers according to the site of the primary or second primary cancer. Given the prevalence of diabetes in patients with cancer, clarifying the impact of coexisting diabetes on the risk of developing second primary cancer is necessary.

The present study aimed to investigate the impact of coexisting diabetes at the time of cancer diagnosis on overall survival and incidence of second primary cancer in patients with cancer in Japan.

MATERIALS AND METHODS

Data sources

The present multicenter retrospective cohort study used population-based data from the Osaka Cancer Registry linked with administrative data. The Osaka Cancer Registry data provide information on cancer diagnosis and survival status for patients residing in Osaka Prefecture, Japan, and include age, sex, type of cancer, date of cancer diagnosis, date of the last follow up, date of death and stage of cancer (i.e., localized, regional to lymph nodes, regional by direct extension or distant). Administrative data were produced under Japan's Diagnosis Procedure Combination Per-Diem Payment System (DPC), which prescribes reimbursements from insurers to acute care hospitals. The DPC data included a history of medications and clinical procedures, and were collected from 36 designated cancer care hospitals in Osaka. Designated cancer care hospitals are medical facilities certified by the national or prefectural government as having advanced competence, experience and leadership in cancer treatment. At the time of admission, data on body height, weight and diagnostic disease name based on the International Classification of Diseases 10th revision codes were recorded in the DPC data. The Osaka Cancer Registry data were linked to the DPC data and anonymized after linkage[19–21]. Analyses were carried out using an anonymized dataset.

Study population

The present study comprised patients diagnosed with cancer between 2010 and 2015. We excluded patients with carcinoma *in situ*, patients with multiple cancers diagnosed with second primary cancer within 2 months of the first cancer diagnosis, patients aged <20 years or >100 years at cancer diagnosis, and death certificate only cases at first cancer diagnosis. The patients were divided into two groups, one with coexisting diabetes and one without coexisting diabetes, according to the presence and timing of diabetes diagnosis. The presence of diabetes was identified from the prescription records of antidiabetic drugs in the DPC data. The earliest date for the prescription of antidiabetic drugs was defined as the timepoint at which the diagnosis of diabetes was confirmed. Antidiabetic drugs included metformin, insulin and insulin analogs (pen-type injection device), glucagon-like peptide 1 receptor agonists, dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter 2 inhibitors, thiazolidines, glinides, alpha-glucosidase inhibitors and sulfonylureas. Patients diagnosed with diabetes in the month after the diagnosis of cancer or later were included in the group without coexisting diabetes.

Statistical analysis

Baseline characteristics of the two groups of patients were compared using the Mann–Whitney test for continuous variables, and χ^2-test for categorical variables. First, we analyzed the effects of diabetes on the overall survival of patients with cancer by comparing patients with cancer and with diabetes at the time of cancer diagnosis with those without diabetes. Patient survival was followed up from the time of diagnosis to May

2019. The Kaplan–Meier method and log-rank test were used to compare overall survival rates for all patients, and for each cancer site with and without diabetes at the time for cancer diagnosis. The analysis was first applied to overall cancers and then replicated for 22 specific cancer sites based on the International Classification of Diseases 10th Revision classification. Next, to investigate the effects of diabetes on overall survival, HRs and 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model adjusted by age category (20–49, 50–59, 60–69, 70–79 and 80–99 years), sex, first cancer site (at the time of analysis for all cancer sites), stage at diagnosis (localized, regional to lymph nodes, regional by direct extension, distant and unknown) and body mass index (BMI) category (<18.5, 18.5–24.9, ≥25.0 kg/m^2 and not measured).

Second, to estimate the impact of diabetes on second primary cancer development, the competing risk analysis was carried out with death as the competing risk. Subdistribution HRs and 95% CIs were calculated using the Fine and Gray model[22]. The first and second primary cancers diagnosed between January 2010 and December 2015 were used. The survival was also censored by December 2015. We assessed proportional hazards assumption by graphical evaluation of log–log plots for the survival analysis. Statistical analyses were carried out using STATA (version 16; StataCorp, College Station, TX, USA).

Ethics approval

The present study was approved by the Institutional Review Board of Osaka International Cancer Institute (approval number: 1707105108), and was carried out in accordance with the ethical standards of the Declaration of Helsinki. We obtained the dataset with no personally identifiable information from the Osaka Cancer Registry, and independently processed it in accordance with the Act on Promotion of Cancer Registries.

RESULTS

Participants and baseline characteristics

Of the 155,796 patients diagnosed with cancer between 2010 and 2015, we excluded 18,700 patients with carcinoma *in situ*, 4,657 patients with multiple cancer diagnosed with second primary cancer within 2 months of the first cancer diagnosis, 682 patients aged <20 years and 35 patients aged >100 years at cancer diagnosis, and 21 death certificate only cases at first cancer diagnosis. In total, 131,701 patients were included in the analysis, of which we identified 6,135 (4.7%) patients with diabetes at the time of cancer diagnosis and compared them with 125,566 (95.3%) patients with no confirmed diagnosis of diabetes at the time of cancer diagnosis (12,543 of whom were diagnosed with diabetes after cancer diagnosis; Figure 1). Compared with patients without diabetes, patients with coexisting diabetes were older at the time of cancer diagnosis (70 years *vs* 73 years), comprised a higher proportion of men (57.0% *vs* 69.8%), had a higher BMI (22.2 kg/m^2 *vs* 23.1 kg/m^2) and had more advanced cancer (distant stage, 19.2% *vs* 26.0%; Table 1). The proportion of patients with liver and pancreatic cancers was higher, and the proportion of patients with breast and uterine cancers was lower in the coexisting diabetes group than in the group without diabetes (Table 2).

Overall survival

The 5-year survival rates for patient with and without coexisting diabetes were 56.2% (95% CI 54.8–57.6) and 72.7% (95% CI 72.4–73.0), respectively (Table 2). Using the Cox proportional hazards model, we estimated HRs of death adjusted for sex, age category, cancer stage, BMI category and cancer site in the coexisting diabetes group with the group without diabetes as the reference (Table 3). The mortality rate was higher in patients with coexisting diabetes than in patients

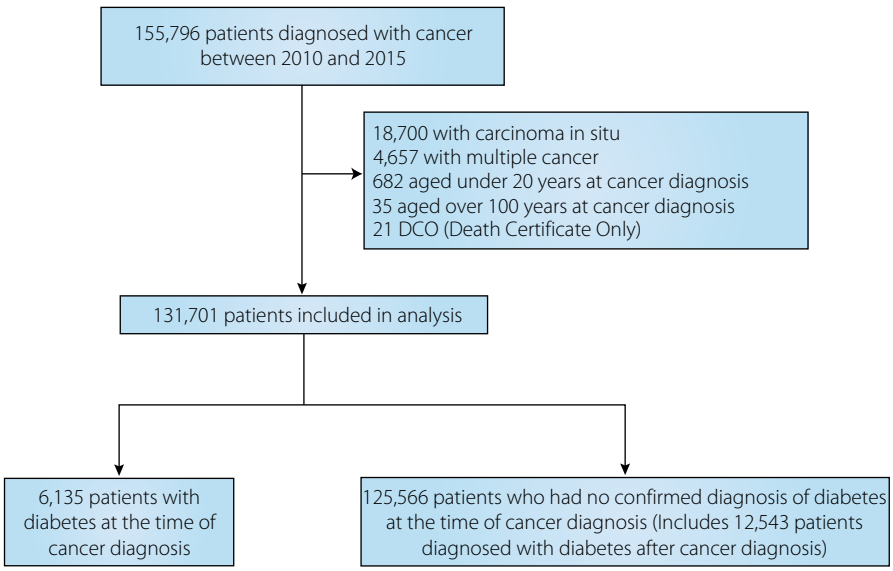

FIGURE 1 | Flowchart of patient selection for analysis among those diagnosed with cancer between 2010 and 2015 in Osaka, Japan.

Table 1 | Baseline characteristics of patients diagnosed with cancer by diabetic status, Osaka, Japan, 2010–2015

	Total	Coexistence with diabetes at cancer diagnosis	No diabetes at cancer diagnosis	*P*-value*
n (%)	131,701 (100.0)	6,135 (4.7)	125,566 (95.3)	
All-cause mortality, *n* (%)	35,168 (26.7)	2,373 (38.7)	32,795 (26.1)	<0.001
Second primary cancer incidence, *n* (%)	4,853 (3.7)	236 (3.9)	4,617 (3.7)	0.491
Male, *n* (%)	75.853 (57.6)	4,281 (69.8)	71,572 (57.0)	<0.001
Age at diagnosis, median (IQR)	70 (62–77)	73 (67–79)	70 (62–77)	<0.001
Age category, *n* (%)				
20–49 years	12,103 (9.2)	113 (1.8)	11,990 (9.6)	<0.001
50–59 years	14,187 (10.8)	377 (6.2)	13,810 (11.0)	
60–69 years	37,552 (28.5)	1,631 (26.6)	35,921 (28.6)	
70–79 years	45,632 (34.7)	2,696 (43.9)	42,936 (34.2)	
80–99 years	22,227 (16.9)	1,318 (21.5)	20,909 (16.7)	
Stage at diagnosis, *n* (%)				
Localized	63,227 (48.0)	2,497 (40.7)	60,730 (48.4)	<0.001
Regional to lymph nodes	13,207 (10.0)	481 (7.8)	12,726 (10.1)	
Regional by direct extension	21,287 (16.2)	1,085 (17.7)	20,202 (16.1)	
Distant	25,682 (19.5)	1,596 (26.0)	24,086 (19.2)	
Unknown	8,298 (6.3)	476 (7.8)	7,822 (6.2)	
BMI (kg/m^2), median (IQR)	22.2 (20.0–24.7)	23.1 (20.5–25.7)	22.2 (19.9–24.6)	<0.001
BMI category				
<18.5	14,330 (10.9)	552 (9.0)	13,778 (11.0)	<0.001
18.5–24.9	72,083 (54.7)	3,336 (54.4)	68,747 (54.8)	
≥25.0	24,644 (18.7)	1,721 (28.1)	22,923 (18.3)	
Not measured	20,644 (15.7)	526 (8.6)	20,118 (16.0)	

Patients with carcinoma *in situ* were excluded. The diagnosis of diabetes mellitus is based on the prescription history of diabetic medications. **P*-values of the Mann–Whitney test for continuous variables and the chi-squared tests for categorical variables. BMI, body mass index; IQR, Interquartile range.

without diabetes, with an adjusted HR for all cancer sites of 1.37 (95% CI 1.31–1.43) in the coexisting diabetes group. Visual inspection of the proportional hazard assumption using a log–log plot showed no signs of violation of the assumption. (Figure S1).

The impact of diabetes on prognosis varied depending on the cancer site. Unadjusted analysis showed that the overall mortality rate in patients with cancer with diabetes was higher for several types of cancers, except cancers of the esophagus, gallbladder, pancreas and uterus (Table 2). Similarly, analysis adjusted for sex, age category, cancer stage and BMI category showed a more than threefold increase in adjusted HR for cancers of the thyroid and ovary, followed by a more than twofold increase in brain/central nervous system, larynx and multiple myeloma. (Table 3). HRs of death for each covariate by univariable and multivariable Cox proportional hazards are shown in Table S1.

Risk of second primary cancer

Of the 125,566 patients without diabetes, 4,617 (3.7%) developed second primary cancer. Of the 6,135 patients with diabetes at the time of cancer diagnosis, 236 (3.9%) developed second primary cancer (Table 1). The subdistribution HR for the risk of developing second primary cancer in the coexisting diabetes group was 1.23 (95% CI 1.08–1.41; Table 4).

For site-specific analysis, we first examined the effect of coexisting diabetes on the risk of second primary cancer for each patient at each primary cancer site. The coexistence of diabetes was associated with a 1.5-fold increase in the subdistribution HR for the risk of second primary cancer in patients with colorectal cancer (adjusted HR 1.52, 95% CI 1.13–2.03). In contrast, in patients with liver cancer, the coexistence of diabetes reduced the risk of developing second primary cancer (adjusted HR 0.27, 95% CI 0.12–0.59; Table 4).

We next examined the association between coexisting diabetes and the risk of developing second primary cancer for each second primary cancer site. In the group with coexisting diabetes, approximately 1.6- to sixfold HRs were observed for developing second primary cancer of multiple myeloma (HR 6.04, 95% CI 2.25–16.21), uterus (HR 2.66, 1.06–6.70), pancreas (HR 1.89, 95% CI 1.09–3.25) and liver (HR 1.60, 95% CI 1.05–2.44; Table 5).

DISCUSSION

To examine the impact of diabetes in patients with cancer, the present study compared patients with cancer without diabetes

Table 2 | Distribution of the number of patients by cancer site and 5-year overall survival

Site of first primary cancer	No. patients (%)	5-year overall survival (95% CI)	*P*-value (log-rank)
All cancer (C00–C96)			
Diabetes	6,135 (100)	56.2 (54.8–57.6)	
No diabetes	125,566 (100)	72.7 (72.4–73.0)	<0.001
Oral cavity/pharynx (C00–C14)			
Diabetes	68 (1.1)	55.4 (41.0–67.7)	
No diabetes	3,347 (2.7)	71.6 (69.9–73.3)	<0.001
Esophagus (C15)			
Diabetes	119 (1.9)	63.0 (52.2–72.1)	
No diabetes	3,993 (3.2)	60.8 (59.1–62.5)	0.922
Stomach (C16)			
Diabetes	926 (15.1)	66.2 (62.6–69.5)	
No diabetes	18,189 (14.5)	73.8 (73.1–74.4)	<0.001
Colorectum (C18–C20)			
Diabetes	890 (14.5)	69.8 (66.4–73.0)	
No diabetes	16,737 (13.3)	78.3 (77.6–78.9)	<0.001
Liver (C22)			
Diabetes	598 (9.8)	48.2 (43.4–52.8)	
No diabetes	6,721 (5.4)	52.2 (50.9–53.6)	0.001
Gallbladder (C23–C24)			
Diabetes	204 (3.3)	38.2 (30.1–46.3)	
No diabetes	2,518 (2.0)	39.2 (36.9–41.4)	0.501
Pancreas (C25)			
Diabetes	749 (12.2)	23.4 (19.4–27.5)	
No diabetes	4,530 (3.6)	27.4 (25.7–29.2)	0.092
Larynx (C32)			
Diabetes	35 (0.6)	75.6 (56.8–87.1)	
No diabetes	1,079 (0.9)	83.1 (80.5–85.4)	0.030
Lung (C33–C34)			
Diabetes	826 (13.5)	35.0 (31.0–39.0)	
No diabetes	14,465 (11.5)	49.9 (48.9–50.8)	<0.001
Skin (C43–C44)			
Diabetes	80 (1.3)	77.6 (65.8–85.7)	
No diabetes	3,082 (2.5)	85.6 (84.1–86.9)	0.014
Breast (C50)			
Diabetes	171 (2.8)	80.9 (73.1–86.7)	
No diabetes	12,184 (9.7)	93.6 (93.1–94.1)	<0.001
Uterus (C53–C55)			
Diabetes	95 (1.6)	84.6 (75.3–90.6)	
No diabetes	5,018 (4.0)	86.8 (85.7–87.7)	0.220
Ovary (C56)			
Diabetes	24 (0.4)	53.5 (30.8–71.8)	
No diabetes	1,528 (1.2)	76.2 (73.9–78.4)	<0.001
Prostate (C61)			
Diabetes	398 (6.5)	84.7 (80.2–88.2)	
No diabetes	11,435 (9.1)	90.9 (90.4–91.5)	<0.001
Kidney/urinary tract (C64–C66, C68)			
Diabetes	166 (2.7)	73.0 (64.9–79.6)	
No diabetes	3,782 (3.0)	76.9 (75.4–78.3)	0.043
Bladder (C67)			
Diabetes	134 (2.2)	62.9 (52.9–71.3)	
No diabetes	2,884 (2.3)	71.1 (69.2–72.8)	0.013
Brain/central nervous system (C70–C72)			
Diabetes	28 (0.5)	9.8 (0.6–34.6)	
No diabetes	627 (0.5)	53.6 (48.7–58.3)	<0.001

Table 2. (*Continued*)

Site of first primary cancer	No. patients (%)	5-year overall survival (95% CI)	*P*-value (log-rank)
Thyroid (C73)			
Diabetes	58 (1.0)	85.7 (73.4–92.6)	
No diabetes	1,997 (1.6)	94.0 (92.8–95.0)	<0.001
Malignant lymphoma (C81–C85, C96)			
Diabetes	230 (3.8)	54.3 (46.9–61.1)	
No diabetes	4,505 (3.6)	74.8 (73.4–76.1)	<0.001
Multiple myeloma (C88–C90)			
Diabetes	47 (0.8)	44.2 (28.4–59.0)	
No diabetes	824 (0.7)	66.5 (62.8–69.8)	<0.001
Leukemia (C91–C95)			
Diabetes	109 (1.8)	34.7 (24.6–45.1)	
No diabetes	1,723 (1.4)	50.3 (47.8–52.9)	0.001
Others			
Diabetes	180 (2.9)	41.1 (32.6–49.4)	
No diabetes	4,398 (3.5)	64.4 (62.9–65.9)	<0.001

95% CI, 95% confidence interval.

Table 3 | Adjusted hazard ratios of coexisting diabetes on all-cause mortality derived from Cox proportional hazards models according to cancer site

Site of first primary cancer	ICD-10	Adjusted HR (95% CI)
All cancer site		1.37 (1.31–1.43)
Oral cavity/pharynx	C00–C14	1.94 (1.30–2.91)
Esophagus	C15	0.92 (0.66–1.28)
Stomach	C16	1.45 (1.28–1.64)
Colorectum	C18–C20	1.55 (1.35–1.77)
Liver	C22	1.20 (1.05–1.36)
Gallbladder	C23–C24	1.01 (0.82–1.24)
Pancreas	C25	1.17 (1.05–1.29)
Larynx	C32	2.10 (1.02–4.32)
Lung	C33–C34	1.60 (1.45–1.77)
Skin	C43–C44	1.78 (1.07–2.96)
Breast	C50	1.91 (1.30–2.81)
Uterus	C53–C55	1.29 (0.75–2.21)
Ovary	C56	3.35 (1.77–6.35)
Prostate	C61	1.43 (1.08–1.89)
Kidney/urinary tract	C64–C66, C68	0.89 (0.65–1.24)
Bladder	C67	1.65 (1.21–2.26)
Brain/central nervous system	C70–C72	2.62 (1.50–4.60)
Thyroid	C73	3.30 (1.57–6.95)
Malignant lymphoma	C81–C85, C96	1.71 (1.38–2.12)
Multiple myeloma	C88–C90	2.04 (1.32–3.18)
Leukemia	C91–C95	1.18 (0.91–1.54)
Others		1.75 (1.41–2.18)

Hazard ratios for the patients with coexisting diabetes at cancer diagnosis are shown with those without coexisting diabetes as reference. All models are adjusted for age category, sex, first cancer site (at the time of analysis for all cancer sites), stage at diagnosis and body mass index category. 95% CI, 95% confidence interval; HR, hazard ratio; ICD-10, International Classification of Diseases 10th Revision.

and those with coexisting diabetes and receiving antidiabetic drug therapy at the time of cancer diagnosis. The coexistence of diabetes was associated with poorer overall survival and a higher risk of developing second primary cancer compared with that in patients without diabetes. The association between coexisting diabetes and the prognosis of patients with cancer has been reported previously[5–11]. Nevertheless, most of these studies are outdated, and do not take into account recent advancements in treatment and improved prognosis. Furthermore, only a few studies have considered cancer stage at diagnosis[5,10]. Among patients with colorectal, breast and uterine cancers, patients with diabetes are more likely to be diagnosed with cancer at a more advanced stage compared with patients without diabetes[10,23]. This might partially explain the association between coexistent diabetes and poor prognosis in patients with cancer. The present study showed that patients with diabetes tended to have more advanced cancers, which is consistent with previous reports[10,23]. Our analysis also showed that diabetes was associated with poor prognosis, even after adjusting for cancer stage. This suggests that other mechanisms might underpin the impact of diabetes on prognosis. In addition to advanced cancer stage, low socioeconomic status[24], high risk of postoperative mortality after cancer surgery[25], high risk of chemotherapy-related toxicity[26], decreased renal function associated with diabetes[27], limited cancer treatment options[10] and increased cardiovascular complications[28–30] have been proposed as mechanisms by which the coexistence of diabetes worsens the prognosis of patients with cancer.

Reports suggest that patients diagnosed with cancer are likely to receive less treatment for diabetes[31]. Inadequate diabetes treatment might increase the risk of diabetic complications and worsen the prognosis of patients with cancer. In patients with

Table 4 | Adjusted hazard ratios of coexisting diabetes on the development of second primary cancer derived from Cox proportional hazards models according to first cancer site

Site of first primary cancer	ICD-10	Subdistribution HR (95%CI)
All cancer site		1.23 (1.08–1.41)
Oral cavity/pharynx	C00–C14	1.29 (0.52–3.17)
Esophagus	C15	0.98 (0.42–2.26)
Stomach	C16	NA
Colorectum	C18–C20	1.52 (1.13–2.03)
Liver	C22	0.27 (0.12–0.59)
Gallbladder	C23–C24	1.05 (0.43–2.58)
Pancreas	C25	0.43 (0.19–1.004)
Larynx	C32	NA
Lung	C33–C34	1.30 (0.90–1.87)
Skin	C43–C44	1.87 (0.84–4.14)
Breast	C50	1.71 (0.75–3.87)
Uterus	C53–C55	1.88 (0.63–5.62)
Ovary	C56	NA
Prostate	C61	NA
Kidney/urinary tract	C64–C66, C68	NA
Bladder	C67	1.09 (0.56–2.13)
Brain/central nervous system	C70–C72	6.11 (0.52–72.26)
Thyroid	C73	1.13 (0.33–3.85)
Malignant lymphoma	C81–C85, C96	0.96 (0.46–2.00)
Multiple myeloma	C88–C90	NA
Leukemia	C91–C95	1.53 (0.34–6.81)
Others		0.90 (0.37–2.22)

Hazard ratios for the patients with coexisting diabetes at cancer diagnosis are shown with those without coexisting diabetes as reference. All models are adjusted for age category, sex, first cancer site (at the time of analysis for all cancer sites), stage at diagnosis, and body mass index category. 95% CI, 95% confidence interval; HR, hazard ratios; ICD-10, International Classification of Diseases 10th Revision; NA, not applicable.

type 2 diabetes without cancer, adequate glycemic control correlates with good prognosis[32]. Furthermore, hyperglycemia and hyperinsulinemia associated with diabetes promote cancer progression[13]. However, the impact of aggressive treatment for diabetes in patients with cancer remains unclear. Further studies are warranted to determine whether optimal management of diabetes improves the prognosis of patients with cancer with coexisting diabetes.

In site-specific analyses, coexisting diabetes was associated with overall survival for many cancer sites, but there were several sites with no strong evidence of association. One explanation for this discrepancy is that for some cancer sites, the effect of coexisting diabetes did not reach statistical significance due to insufficient sample size. Another potential explanation is that the effect of diabetes on survival was not apparent in patients with cancer sites associated with poor prognosis. As patients with poor prognosis are more likely to die from cancer than from comorbidities, the impact of diabetes on mortality might be relatively small. Thus, the impact of coexisting diabetes on overall survival might not be apparent in populations with poor prognosis. In this regard, cancers of the gallbladder (unadjusted and adjusted analysis) and pancreas (unadjusted analysis) fall into this category, as historical Japanese statistics show that these cancers have the poorest prognosis[33,34]. In a meta-analysis by Barone *et al.*[5], the prognosis of patients with pancreatic cancer was not associated with the coexistence of diabetes. In addition, Mao *et al.*[35] reported that coexisting diabetes was associated with poor prognosis in patients with pancreatic cancer, but not in a subgroup of patients with cancer at an unresectable stage. Similarly, the lack of an association between coexisting diabetes and prognosis in patients with pancreatic and gallbladder cancers in the present analysis might be underscored by the generally poor prognosis of these cancer types. In contrast, for cancers of sites with favorable 5-year survival rates according to Japanese statistics[33] (prostate, thyroid, skin, breast, laryngeal, uterine, bladder, colorectal, kidney/urinary tract, gastric and ovarian cancers, and malignant lymphoma), a moderate association was observed between coexisting diabetes and prognosis for all sites, except uterine and kidney/urinary tract cancers. This suggests that the effects of coexisting diabetes are more likely to become apparent in cancer types with a favorable prognosis.

The present study showed that coexisting diabetes was associated with the development of second primary cancer in patients on antidiabetic drug therapy. Accordingly, it is critical to carefully screen patients with cancer with coexisting diabetes for second primary cancers. In site-specific analysis of primary cancer sites of patients developing a second primary cancer,

Table 5 | Adjusted hazard ratios of coexisting diabetes on the development of second primary cancer derived from Cox proportional hazards models according to second cancer site

Site of first primary cancer	ICD-10	Subdistribution HR (95% CI)
All cancer site		1.23 (1.08–1.41)
Oral cavity/pharynx	C00–C14	0.83 (0.34–2.05)
Esophagus	C15	0.93 (0.46–1.89)
Stomach	C16	0.99 (0.71–1.39)
Colorectum	C18–C20	1.13 (0.78–1.62)
Liver	C22	1.60 (1.05–2.44)
Gallbladder	C23–C24	1.41 (0.65–3.08)
Pancreas	C25	1.89 (1.09–3.25)
Larynx	C32	1.24 (0.31–5.01)
Lung	C33–C34	0.81 (0.56–1.16)
Skin	C43–C44	1.27 (0.58–2.78)
Breast	C50	0.90 (0.36–2.25)
Uterus	C53–C55	2.66 (1.06–6.70)
Ovary	C56	NA
Prostate	C61	0.58 (0.33–1.04)
Kidney/urinary tract	C64–C66, C68	1.12 (0.57–2.17)
Bladder	C67	1.04 (0.48–2.28)
Brain/central nervous system	C70–C72	3.63 (0.79–16.63)
Thyroid	C73	0.66 (0.16–2.74)
Malignant lymphoma	C81–C85, C96	NA
Multiple myeloma	C88–C90	6.04 (2.25–16.21)
Leukemia	C91–C95	2.17 (0.84–5.61)
Others		1.24 (0.58–2.66)

HRs for the patients with coexisting diabetes at cancer diagnosis are shown with those without coexisting diabetes as reference. All models are adjusted by age category, sex, first cancer site, stage at diagnosis, and body mass index category. 95%CI, 95% confidence interval; HR, hazard ratios; ICD, International Classification of Disease 10th Revision; NA, not applicable.

coexisting diabetes was associated with an increased incidence of second primary cancers in patients with colorectal cancers, whereas coexisting diabetes was associated with a decreased risk of developing second primary cancers in patients with liver cancer. Patients with liver cancer with diabetes have a poor prognosis and might be less likely to develop a second primary cancer. First, liver cancer generally has a high recurrence rate. In addition, the coexistence of diabetes in patients with liver cancer might be highly correlated with the complication of cirrhosis, which has a poor prognosis. Thus, patients with liver cancer are more likely to be exposed to recurrence or progression of liver cancer and associated death, and might have a relatively low risk of developing another second primary cancer. In site-specific analysis of second primary cancers, the group with coexisting diabetes had an increased risk of developing second primary cancers of multiple myeloma, and the cancer of the uterus, pancreas and liver. Similar to the present findings, previous studies examining the risk of developing cancer have reported that diabetes increases the risk of developing liver and uterine cancers[36,37]. Furthermore, obesity is a risk factor for the development of multiple myeloma[38,39]. Thus, the sites of second primary cancers with increased risk in patients with cancer with coexisting diabetes show the same pattern as that of the sites of primary cancers with increased risk in patients with diabetes, implying common pathophysiological mechanisms.

A strength of the present study was its focus on Asians. The pathogenesis of diabetes differs between Asians and white people[12], and the effect of diabetes on the prognosis of patients with cancer might also differ between Asians and white people. Therefore, examining the impact of diabetes using data from the Japanese populations might facilitate more understanding of the prognosis of patients with cancer with coexisting diabetes, in consideration of ethnic differences. In this study, the point estimate of the adjusted HR for mortality was 1.37, which approximates the value of 1.41 reported by Barone *et al.*[5] In sum, this study suggests that the impact of coexisting diabetes on prognosis in patients with cancer is similar between Asians and white people.

The present study had some limitations. First, the coexistence of diabetes was identified based on drug prescription records in the DPC. It is unclear whether all patients with diabetes could be extracted purely based on prescription history. However, the diagnosis of diabetes is likely to be valid for patients who have been prescribed antidiabetic drugs. The majority of misclassifications are considered to comprise one of the following: (i) patients with diabetes who did not have any prescription history of antidiabetic drugs in the DPC data could have been

categorized into the group of patients without diabetes; and (ii) patients with diabetes before cancer diagnosis were misclassified as patients with newly developed diabetes after cancer diagnosis. Such misclassifications are considered to constitute a source of bias in the direction of weakening the effects of diabetes. Second, there were confounding factors that were not accounted for in the present study and warrant further investigation. For example, the effect of comorbidities other than diabetes on survival and risk of developing second primary cancers was not examined in this study. In addition, cancer treatment, severity of diabetes, type of diabetes treatments and diabetic complications were also not considered, and may might affected the results. Furthermore, to evaluate potential multicollinearity in the multivariable analysis, we carried out Spearman's correlation analysis of each variable and the comorbidity of diabetes at the time of cancer diagnosis, and confirmed that the absolute value of the correlation coefficient was <0.1 for all variables (data not shown). Finally, data on the details of the cause of death were not examined, and cancer-related deaths and non-cancer-related deaths were not distinguished. Therefore, we were unable to examine the effects of second primary cancers on the prognosis of patients with cancer.

In conclusion, coexisting diabetes was associated with poorer prognosis and an increased incidence of second primary cancers in Japanese patients with cancer and receiving antidiabetic drug therapy. The efficacy of diabetes prevention and treatment for improving the prognosis of patients with cancer remains a subject for future studies.

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DISCLOSURE

The authors declare no conflict of interest.
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REFERENCES

1. Kotwas A, Karakiewicz B, Zabielska P, *et al*. Epidemiological factors for type 2 diabetes mellitus: Evidence from the global burden of disease. *Arch Public Health* 2021; 79: 110.
2. Centers for Disease Control and Prevention national diabetes statistics report. Atlanta, Georgia: Centers for Disease Control and Prevention, U.S, Dept of Health and Human Services, 2020.
3. Ministry of Health, Labour and Welfare of Japan. The National Health and Nutrition Survey in Japan. 2016. Available from: http://www.mhlw.go.jp/bunya/kenkou/eiyou/h28-houkoku.html Accessed April 18, 2022. In Japanese
4. Giovannucci E, Harlan DM, Archer MC, *et al*. Diabetes and cancer: A consensus report. *CA Cancer J Clin* 2010; 60: 207–221.
5. Barone BB, Yeh HC, Snyder CF, *et al*. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: A systematic review and meta-analysis. *JAMA* 2008; 300: 2754–2764.
6. Lipscombe LL, Goodwin PJ, Zinman B, *et al*. The impact of diabetes on survival following breast cancer. *Breast Cancer Res Treat* 2008; 109: 389–395.
7. Ranc K, Jørgensen ME, Friis S, *et al*. Mortality after cancer among patients with diabetes mellitus: Effect of diabetes duration and treatment. *Diabetologia* 2014; 57: 927–934.
8. Renehan AG, Yeh HC, Johnson JA, *et al*. Diabetes and cancer (2): Evaluating the impact of diabetes on mortality in patients with cancer. *Diabetologia* 2012; 55: 1619–1632.
9. Stein KB, Snyder CF, Barone BB, *et al*. Colorectal cancer outcomes, recurrence, and complications in persons with and without diabetes mellitus: A systematic review and meta-analysis. *Dig Dis Sci* 2010; 55: 1839–1851.
10. Van De Poll-Franse LV, Houterman S, Janssen-Heijnen MLG, *et al*. Less aggressive treatment and worse overall survival in cancer patients with diabetes: A large population based analysis. *Int J Cancer* 2007; 120: 1986–1992.
11. Peairs KS, Barone BB, Snyder CF, *et al*. Diabetes mellitus and breast cancer outcomes: A systematic review and meta-analysis. *J Clin Oncol* 2011; 29: 40–46.
12. Kodama K, Tojjar D, Yamada S, *et al*. Ethnic differences in the relationship between insulin sensitivity and insulin response: A systematic review and meta-analysis. *Diabetes Care* 2013; 36: 1789–1796.
13. Duan W, Shen X, Lei J, *et al*. Hyperglycemia, a neglected factor during cancer progression. *Biomed Res Int* 2014; 2014: 461917.
14. Travis LB, Demark Wahnefried WD, Allan JM, *et al*. Aetiology, genetics and prevention of secondary neoplasms in adult cancer survivors. *Nat Rev Clin Oncol* 2013; 10: 289–301.
15. Tabuchi T, Ito Y, Ioka A, *et al*. Incidence of metachronous second primary cancers in Osaka, Japan: Update of analyses using population-based cancer registry data. *Cancer Sci* 2012; 103: 1111–1120.
16. Sung H, Hyun N, Leach CR, *et al*. Association of first primary cancer with risk of subsequent primary cancer among

survivors of adult-onset cancers in the United States. *JAMA* 2020; 324: 2521–2535.
17. Halamkova J, Kazda T, Pehalova L, *et al*. The impact of diabetes mellitus on the second primary malignancies in colorectal cancer patients. *Front Oncol* 2020; 10(January): 573394.
18. Takeuchi D, Koide N, Komatsu D, *et al*. Relationships of obesity and diabetes mellitus to other primary cancers in surgically treated gastric cancer patients. *Int J Surg* 2014; 12: 587–593.
19. Morishima T, Sato A, Nakata K, *et al*. Barthel index-based functional status as a prognostic factor in young and middle-aged adults with newly diagnosed gastric, colorectal and lung cancer: A multicentre retrospective cohort study. *BMJ Open* 2021; 11: 1–10.
20. Nishikawa T, Morishima T, Okawa S, *et al*. Multicentre cohort study of the impact of percutaneous coronary intervention on patients with concurrent cancer and ischaemic heart disease. *BMC Cardiovasc Disord* 2021; 21: 177.
21. Morishima T, Matsumoto Y, Koeda N, *et al*. Impact of comorbidities on survival in gastric, colorectal, and lung cancer patients. *J Epidemiol* 2019; 29: 110–115.
22. van Vugt JLA, Alferink LJM, Buettner S, *et al*. A model including sarcopenia surpasses the MELD score in predicting waiting list mortality in cirrhotic liver transplant candidates: A competing risk analysis in a national cohort. *J Hepatol* 2018; 68: 707–714.
23. Lipscombe LL, Fischer HD, Austin PC, *et al*. The association between diabetes and breast cancer stage at diagnosis: A population-based study. *Breast Cancer Res Treat* 2015; 150: 613–620.
24. Rawshani A, Svensson AM, Zethelius B, *et al*. Association between socioeconomic status and mortality, cardiovascular disease, and cancer in patients with type 2 diabetes. *JAMA Intern Med* 2016; 176: 1146–1154.
25. Barone BB, Yeh HC, Snyder CF, *et al*. Postoperative mortality in cancer patients with preexisting diabetes: Systematic review and meta-analysis. *Diabetes Care* 2010; 33: 931–939.
26. Srokowski TP, Fang S, Hortobagyi GN, *et al*. Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. *J Clin Oncol* 2009; 27: 2170–2176.
27. Zylla D, Gilmore G, Eklund J, *et al*. Impact of diabetes and hyperglycemia on health care utilization, infection risk, and survival in patients with cancer receiving glucocorticoids with chemotherapy. *J Diabetes Complications* 2019; 33: 335–339.
28. Phillips WJ, Johnson C, Law A, *et al*. Comparison of Framingham risk score and chest-CT identified coronary artery calcification in breast cancer patients to predict cardiovascular events. *Int J Cardiol* 2019; 289: 138–143.
29. Morrish NJ, Wang SL, Stevens LK, *et al*. Mortality and causes of death in the WHO multinational study of vascular disease in diabetes. *Diabetologia* 2001; 44(suppl. 2): S14–S21.
30. Sattar N, Rawshani A, Franzén S, *et al*. Age at diagnosis of type 2 diabetes mellitus and associations with cardiovascular and mortality risks. *Circulation* 2019; 139: 2228–2237.
31. Pinheiro LC, Soroka O, Kern LM, *et al*. Diabetes care management patterns before and after a cancer diagnosis: A SEER-Medicare matched cohort study. *Cancer* 2020; 126: 1727–1735.
32. Laiteerapong N, Ham SA, Gao Y, *et al*. The legacy effect in type 2 diabetes:Impactofearlyglycemic control on future complications (the Diabetes & Aging study). *Diabetes Care* 2019; 42: 416–426.
33. Center for Cancer Control and Information Services, National Cancer Center. Monitoring of Cancer Incidence in Japan - Survival 2009-2011 report. 2020. Available from: https://ganjoho.jp/reg_stat/statistics/data/dl/en.html. Accessed April 18, 2022. In Japanese.
34. Matsuda T, Ajiki W, Marugame T, *et al*. Population-based survival of cancer patients diagnosed between 1993 and 1999 in Japan: A chronological and international comparative study. *Jpn J Clin Oncol* 2011; 41: 40–51.
35. Mao Y, Tao M, Jia X, *et al*. Effect of diabetes mellitus on survival in patients with pancreatic cancer: A systematic review and meta-analysis. *Sci Rep* 2015; 5(March): 17102.
36. Vigneri P, Frasca F, Sciacca L, *et al*. Diabetes and cancer. *Endocr Relat Cancer* 2009; 16: 1103–1123.
37. Harding JL, Shaw JE, Peeters A, *et al*. Cancer risk among people with type 1 and type 2 diabetes: Disentangling true associations, detection bias, and reverse causation. *Diabetes Care* 2015; 38: 264–270.
38. Alexander DD, Mink PJ, Adami HO, *et al*. Multiple myeloma: A review of the epidemiologic literature. *Int J Cancer* 2007; 120(suppl. 12): 40–61.
39. Wallin A, Larsson SC. Body mass index and risk of multiple myeloma: A meta-analysis of prospective studies. *Eur J Cancer* 2011; 47: 1606–1615.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Hazard ratios for all-cause mortality for each covariate from univariable and multivariable Cox proportional hazards models.

Figure S1 | Visual inspection of the proportional hazard assumption using a log–log plot.