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Burden of cancer associated with type 2 diabetes mellitus in Japan, 2010–2030

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Key words

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Diabetes mellitus constitutes a major disease burden globally, and the prevalence of diabetes continues to increase worldwide. We aimed to estimate the burden of cancer associated with type 2 diabetes mellitus in Japan between 2010 and 2030. In this study, we estimated the population attributable fraction of cancer risk associated with type 2 diabetes in 2010 and 2030 using the prevalence estimates of type 2 diabetes in Japan from 1990 to 2030, summary hazard ratios of diabetes and cancer risk from a pooled analysis of eight large-scale Japanese cohort studies, observed incidence/mortality of cancer in 2010 and predicted incidence/mortality for 2030 derived from the age–period–cohort model. Our results showed that between 2010 and 2030, the total numbers of cancer incidence and mortality were predicted to increase by 38.9% and 10.5% in adults aged above 20 years, respectively. In the number of excess incident cancer cases associated with type 2 diabetes, an increase of 26.5% in men and 53.2% in women is expected between 2010 and 2030. The age-specific analysis showed that the population attributable fraction of cancer will increase in adults aged >60 years over time, but will not change in adults aged 20–59 years. In conclusion, this study suggests a modest but steady increase in cancers associated with type 2 diabetes.

Diabetes mellitus is one of the most frequent chronic diseases worldwide and constitutes a major health burden in terms of mortality and impaired quality of life,[1] essentially through cardiovascular, renal, and neurological complications. The rapidly increasing prevalence of type 2 diabetes, due in particular to population aging and sedentary lifestyle, has important consequences: according to recent studies, between four and five million deaths could be attributed each year to diabetes since the beginning of the decade[2,3] and the number of disability-adjusted life years lost due to diabetes was estimated to have increased by 30% between 1990 and 2010.[4] Japan is expected to follow the global trend, with the overall prevalence increasing from 7.9% in 2010 to 9.8% in 2030.[5]

In recent years, it has been hypothesized that type 2 diabetes might also be associated with an increased occurrence of various cancers.[6] Several meta-analyses of observational studies have shown a significant association between diabetes and total cancer,[7,8] as well as colon,[7,8] liver,[7,8] pancreas,[7,9,10] kidney,[11] bladder,[12] breast,[13] and corpus uteri[14] cancers. A pooled analysis of studies carried out in the Japanese population also reported a positive association between diabetes and bile duct cancer in men, and oesophageal and cervical cancers in women.[8] Furthermore, diabetes might also be associated with an increased risk of lymphoma (non-Hodgkin's and Hodgkin's lymphomas).[15–17] Although the biological mechanisms underlying the relationship between diabetes and cancer are not fully understood, these studies suggest that controlling the current diabetes epidemic might also contribute to cancer prevention. It is thus important to quantify the cancer burden associated with type 2 diabetes, particularly in aging societies. To date, only two studies have reported population attributable fractions (PAF) for the relationship between diabetes and cancer. Lam *et al.*[7] estimated the PAFs for pancreatic, liver, and colorectal cancer mortality across countries of the Asia-Pacific region; Lin *et al.*[18] estimated the PAFs for the incidence of various cancers in Taiwan. However, despite the growing prevalence of type 2 diabetes, no studies have predicted the PAFs of diabetes for cancer.

In this study, we aimed to estimate the burden of cancer associated with type 2 diabetes in Japan in 2010 and 2030, expressed in PAFs. Moreover, we estimated the corresponding numbers of excess cancer cases for cancer sites identified as associated with diabetes.[8] These estimates might contribute to the assessment of the importance of lifestyle modification as an important component of cancer prevention strategies in a rapidly aging country.

Materials and Methods

Data sources. Data on the cancer incidence in Japan from 1980 to 2011 were obtained from the national estimates in

7–32 prefectures in the cancer registry published by the Japan Cancer Surveillance Research Group as part of the Monitoring of Cancer Incidence in Japan Project.[19] We classified the cancer cases in 2010 by cancer type, sex, and 5-year age group according to the International Standard Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), with the morphology code of the International Classification of Disease for Oncology, 3rd Edition (ICD-O-3). Age- and sex-specific cancer mortality data from 1980 to 2013 were obtained from the vital statistics of Japan with permission from the Japanese Ministry of Health, Labor and Welfare.[20]

Predicted cancer incidence and mortality in Japan in 2030. Age–period–cohort (APC) models were used to predict cancer incidence and mortality by cancer site in 2030.[21] We

Table 1. Incidence and mortality of total cancer and cancer sites associated with type 2 diabetes in Japan, 2010 and 2030

Cancer site	ICD-10	Incidence, 2010		Predicted incidence,† 2030		Mortality, 2010		Predicted mortality,† 2030	
		Number of cases	Age-adjusted rate‡	Number of cases	Age-adjusted rate‡	Number of deaths	Age-adjusted rate‡	Number of deaths	Age-adjusted rate‡
Men, aged ≥20 years									
All sites	C00–C96	466 731	595.1	612 500	610.4	211 148	252.7	219 300	179.2
Oesophagus	C15	18 142	23.7	24 400	26.1	9992	12.6	8700	8.5
Colon	C18	42 105	53.8	48 200	46.8	14 943	17.8	18 500	14.4
Rectum	C19–C20	25 946	35.4	32 500	36.7	8973	11.4	10 400	9.5
Liver	C22	31 223	39.7	23 800	24.9	21 502	26.4	12 400	11.4
Bile duct	C23–C24	11 345	13.3	15 600	12.5	8440	9.6	9500	6.9
Pancreas	C25	16 838	21.1	20 800	19.3	14 568	18.0	19 200	17.2
Kidney	C64–C66, C68	14 198	19.2	26 600	29.9	4920	5.8	6900	5.8
Bladder	C67	14 729	17.8	18 700	15.5	4718	5.1	6700	4.3
Lymphoma	C81–85, C96	13 711	18.9	22 000	24.6	5696	6.9	7000	5.6
Diabetes prevalence§		9.86% (2010)		13.10% (2030)					
Women, aged ≥20 years									
All sites	C00–C96	336 065	400.9	502 600	502.7	141 854	127.2	170 800	106.4
Oesophagus	C15	3282	3.4	5400	4.6	1875	1.7	2800	2.0
Colon	C18	36 764	35.7	47 300	33.6	15 093	12.0	20 000	10.2
Rectum	C19–C20	14 154	16.0	16 800	16.1	5222	4.8	6200	3.9
Liver	C22	15 979	14.1	12 600	8.2	11 250	8.9	7000	3.7
Bile duct	C23–C24	11 291	8.6	12 100	6.3	9145	6.5	8700	4.1
Pancreas	C25	15 482	13.9	23 800	15.4	13 447	11.4	21 300	12.3
Breast	C50	68 069	108.5	109 900	145.8	12 454	16.5	14 100	16.8
Corpus uteri	C54	11 793	18.7	27 900	40.7	1854	2.1	3200	3.2
Kidney	C64–C66, C68	6876	3.7	10 700	8.5	2631	1.3	3600	1.9
Bladder	C67	4482	7.2	6900	4.0	2084	2.1	3400	1.4
Lymphoma	C81–85, C96	9964	11.5	14 100	13	4494	3.7	6100	3.4
Diabetes prevalence§		6.06% (2010)		6.69% (2030)					
Both sexes combined, aged ≥20 years									
All sites	C00–C96	802 796	507.3	1 115 100	575.3	353 002	192.7	390 100	147.7
Oesophagus	C15	21 424	13.4	29 800	15.5	11 867	7.0	11 500	5.3
Colon	C18	78 869	46.4	95 500	42.0	30 036	15.5	38 500	13.0
Rectum	C19–C20	40 100	26.2	49 300	27.0	14 195	8.3	16 600	6.8
Liver	C22	47 202	27.4	36 400	17.1	32 752	17.9	19 400	7.8
Bile duct	C23–C24	22 636	14.4	27 700	9.8	17 585	8.4	18 200	5.7
Pancreas	C25	32 320	18.2	44 600	18.3	28 015	15.3	40 500	15.5
Kidney	C64–C66, C68	21 074	13.4	37 300	19.7	7551	4.0	10 500	3.9
Bladder	C67	19 211	10.5	25 600	9.8	6802	3.1	10 100	2.9
Lymphoma	C81–85, C96	23 675	15.8	36 100	19.7	10 190	5.4	13 100	4.7
Diabetes prevalence§		7.89% (2010)		9.75% (2030)					

†Age–period–cohort models were used to predict the incidence and mortality of total and site-specific cancer. ‡Age-adjusted rates are expressed per 100 000. §Source: Charvat H, Goto A, Goto M, *et al.* Impact of population aging on trends in diabetes prevalence: A meta-regression analysis of 160 000 Japanese adults. *Journal of Diabetes Investigation* 2015; 6: 533–42. ICD-10, International Standard Classification of Diseases and Related Health Problems, 10th Revision.

used a modification of the APC model proposed by Moller *et al.* in which the log link function is replaced by the so-called "power 5" link function, as this was shown to improve the accuracy of the projections.[21,22] We fitted the model to the observed incidence starting from 1980 to 2011 and mortality starting from 1980 to 2013 by 5-year periods and 5-year age groups by sex, and projected the linear time trend with adjustment for period and cohort effects to predict the incidence and mortality from 2015–2019 to 2030–2034 by 5-year periods. Our assumption was that a cohort effect of a new generation entering into the projection period will remain the same as the last observed estimates throughout the projected years. For the last observed interval (2010–2014), we used the average number of cases from the available time points to estimate the 5-year incidence and mortality. For those aged below 20 years, we forecasted the future incidence and mortality using the average rates obtained from the previous 10-year interval (2005–2009 and 2010–2014). A projection for the year 2030 was obtained by calculating the yearly average of cancer incidence and mortality between 2030 and 2034. For the age-adjusted cancer incidence and mortality rates, we used the 1985 Japanese standard population for age standardization. All analyses were carried out with R statistical software version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria); in particular, the R package "nordpred" was used for fitting the APC models.

Population attributable fraction estimates. The PAF is an epidemiological tool used to estimate the impact of exposure to a

Table 2. Population attributable fraction (PAF) of cancer incidence attributable to type 2 diabetes by site of cancer in Japan, 2010 and 2030

Cancer site	Attributable fraction, 2010			Preventable fraction, 2030		
	PAF, %	95% CI	Excess attributable cases	PAF, %	95% CI	Excess attributable cases
Men, aged ≥20 years						
Esophagus†	0.5	(−1.8, 3.5)	–	0.7	(−2.3, 4.5)	–
Colon	4.5	(2.6, 6.9)	1907	5.8	(3.3, 8.8)	2786
Rectum†	0.4	(−1.6, 2.9)	–	0.5	(−2.1, 3.8)	–
Liver	9.3	(6.4, 12.8)	2910	11.7	(8.1, 16.1)	2791
Bile duct	4.1	(0.6, 8.7)	462	5.2	(0.8, 10.9)	810
Pancreas	5.6	(2.4, 9.6)	939	7.1	(3.1, 12.1)	1475
Kidney†	3.8	(−2.8, 16.0)	–	4.9	(−3.6, 19.8)	–
Bladder†	2.4	(−0.9, 7.0)	–	3.1	(−1.2, 8.9)	–
Lymphoma†	5.7	(−0.5, 15.3)	–	7.2	(−0.6, 19.0)	–
Total (diabetes-related sites)			6218			7862
All cancer incidence	1.7	(1.2, 2.3)		2.2	(1.6, 3.0)	
Women, aged ≥20 years						
Esophagus	16.6	(0.6, 50.5)	545	18.8	(0.7, 54.3)	1015
Colon†	−0.4	(−1.9, 1.6)	–	−0.5	(−2.2, 1.8)	–
Rectum†	2.5	(−1.3, 9.3)	–	3.0	(−1.5, 10.8)	–
Liver	4.3	(1.6, 8.1)	687	5.0	(1.9, 9.4)	630
Bile duct†	2.0	(−0.8, 6.3)	–	2.3	(−1.0, 7.4)	–
Pancreas	6.4	(1.8, 13.5)	991	7.4	(2.1, 15.5)	1761
Breast†	−0.1	(−1.8,2.1)	–	−0.2	(−2.1, 2.4)	–
Uterus corpus†	3.6	(−0.7, 11.2)	–	4.2	(−0.9, 12.9)	–
Kidney†	1.5	(−3.0, 12.3)	–	1.7	(−3.6, 14.1)	–
Bladder†	2.4	(−1.9, 10.8)	–	2.8	(−2.3, 12.4)	–
Lymphoma†	5.9	(−0.6, 19.1)	–	6.8	(−0.7, 21.6)	–
Total (diabetes-related sites)			2223			3406
All cancer incidence	1.0	(0.4, 1.6)		1.1	(0.5, 1.9)	
Both sexes combined, aged ≥20 years						
Esophagus†	0.3	(−1.8, 3.1)	–	0.3	(−2.3, 3.8)	–
Colon	2.2	(1.0, 3.6)	1735	2.7	(1.3, 4.4)	2579
Rectum†	0.7	(−1.0, 2.7)	–	0.8	(−1.2, 3.3)	–
Liver	7.2	(4.9, 10.0)	3399	8.8	(6.0, 12.1)	3203
Bile duct†	1.9	(−0.2, 4.5)	–	2.3	(−0.2, 5.6)	–
Pancreas	5.5	(3.3, 8.2)	1778	6.7	(4.0, 10.0)	2988
Breast†	2.0	(−1.5, 7.3)	–	2.4	(−1.9, 8.9)	–
Uterus corpus†	3.6	(−0.7, 11.2)	–	4.2	(−0.9, 12.9)	–
Kidney†	2.9	(−1.7, 10.8)	–	3.6	(−2.1, 13.1)	–
Bladder†	1.5	(−1.0, 4.9)	–	1.8	(−1.3, 6.0)	–
Lymphoma†	2.2	(−1.2, 7.2)	–	2.7	(−1.5, 8.7)	–
Total (diabetes-related sites)			6912			8770
All cancer incidence	1.4	(1.0, 1.8)	11 239	1.7	(1.2, 2.2)	18 957

†Summary relative risks in the pooled analysis of Japanese cohorts were not significant for the corresponding sites. –, Not applicable. CI, confidence interval.

risk factor on the occurrence of a particular disease at the population level by combining information on the magnitude of the relationship between the risk factor and the disease as well as information on the distribution of exposure to the risk factor in the population of interest.[23] In this work, sex-specific PAFs were used to quantify the impact of diabetes on the occurrence of cancer in the Japanese adult population in 2010 and 2030. For a given cancer site, PAF calculations were based on the following formula:

$$\mathrm{PAF} = \frac{p(\mathrm{RR}-1)}{p(\mathrm{RR}-1)+1} \quad (1)$$

where p represents the prevalence of diabetes in the population and RR is an estimate of the relative risk of the association between diabetes and the particular cancer under study. Estimates of the prevalence of diabetes in the Japanese adult population were obtained from the recently published meta-regression analysis[5] and adjusted hazard ratio estimates were obtained from the meta-analysis of the association between diabetes and various cancer sites based on eight large-scale cohort studies carried out in Japan.[8] Because the effect of risk factors on the occurrence of cancer is due to long-term alterations of biological mechanisms, the clinical manifestations of cancer appear years after the initial exposure; this latency period has been estimated to be approximately 15 years.[22] Accordingly, PAF estimates for 2010 and 2030 were based on prevalence estimates of diabetes for the years 1995 and 2015, respectively. Confidence intervals for PAF estimates were obtained by simulation. For a given year, a given cancer site and a given gender, we used the following procedure: (i) we drew a sample from the age category-specific distribution of the meta-regression model parameters (assumed to be multivariate normal) and computed the corresponding age-standardized diabetes prevalence; (ii) drew a sample from the distribution (assumed to be normal) of the meta-analysis parameters and computed the corresponding hazard ratio of the association between diabetes and cancer; and (iii) used formula[1] to calculate the PAF. This procedure was repeated 20 000 times and confidence intervals were then obtained by taking the 2.5 and 97.5 percentiles of the resulting empirical PAF distribution. The estimated numbers of incident cancer cases attributable to diabetes were then obtained by multiplying the PAF estimate for a given year by the estimated number of incident cancer cases for the same year. We applied the age-specific PAFs and the age-specific prevalence estimates to calculate the ratios of the excess attributable cases by age group.

Sensitivity analysis. Unlike other common risk factors, the latency period between exposure to cancer occurrence has not been clearly established for type 2 diabetes. To check the robustness of our PAF estimation, we carried out a sensitivity analysis with differing latency periods (10 and 20 years). Accordingly, the PAF for 2010 were estimated using prevalence estimates of diabetes for the years 1990 and 2000, and the PAF for 2015 using the prevalence of diabetes for the years 2010 and 2020.

Results

Between 2010 and 2030, the total numbers of cancer incidence and mortality were predicted to increase by 31.2% and 3.9% in men aged 20 years or older, respectively (Table 1). Women aged 20 years or older showed the same propensity, with the number of total cancer incidence increasing by 49.6% and that of mortality by 20.4%. The age-adjusted incidence rate for all sites for adult men showed a slight increase (595.1 in 2010 to 610.4 in 2030 per 100 000). However, a decrease was noted for the age-adjusted total cancer mortality rate in adult men (252.7 in 2010 to 179.2 in 2030 per 100 000). The age-adjusted cancer incidence rate for adult women showed an increase (400.9 in 2010 to 502.7 in 2030 per 100 000), but the mortality rate was predicted to fall in 20 years (127.2 in 2010 to 106.4 in 2030 per 100 000).

Table 2 shows the PAFs associated with type 2 diabetes as well as the estimated number of excess incident cases for corresponding cancer sites. Between 2010 and 2030, the PAF of all cancer incidence was predicted to increase modestly from 1.4% in 2010 to 1.7% in 2030. The site-specific PAF of cancer showed a modest increase in colon (4.5–5.8%), liver (9.3–11.7%), bile duct (4.1–5.2%), and pancreatic cancer (5.6–7.1%) among men. The PAF of cancer in women showed a similar trend in oesophagus (16.6–18.8%), liver (4.3–5.0%), and pancreatic cancer (6.4–7.4%). In terms of the number of excess incident cancer cases, an increase of 26.5% between 2010 and 2030 is expected for men (from 6218 to 7862 cases) and an increase of 53.2% in women (from 2223 to 3406 cases). Ratios of the excess cancer cases associated with type 2 diabetes disaggregated by age group showed that the increase in cancer associated with diabetes in people aged 70 years and over contributed predominantly to such increase over years (Fig. 1). The PAFs of cancer by age group (Table 3) showed an increase in men aged 60 years and over, whereas women aged 60 years and over showed no significant change in PAF for the same period. The PAFs in both men

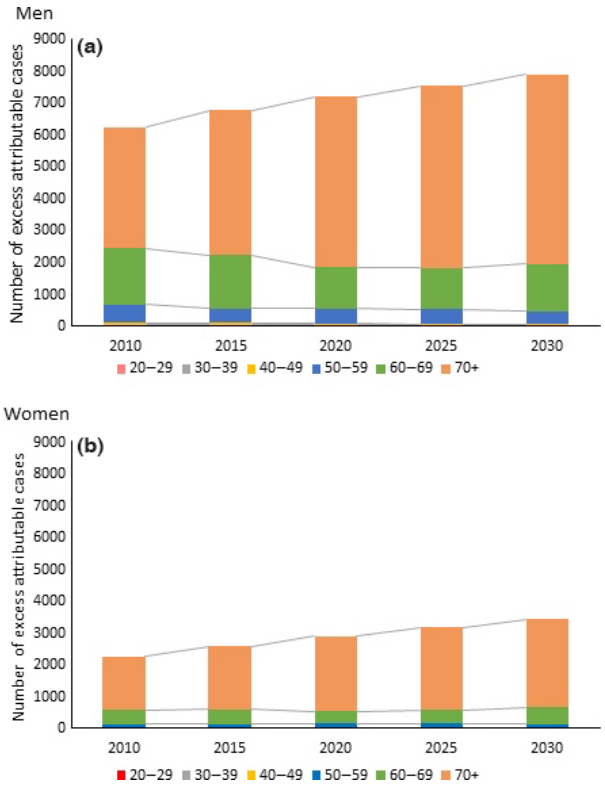

Fig. 1. Fraction of incident cancer cases attributable to diabetes in Japan by age group, 2010–2030. Note that the diabetic patients aged between 20 and 49 years in the corresponding years are projected to have only a limited number of incident cancer cases.

Table 3. Population attributable fraction (PAF) for cancer associated with type 2 diabetes by site and age group in Japan, 2010 and 2030

Age group	Oesophagus†		Colon‡		Liver		Bile duct‡		Pancreas	
	PAF (%)	(95% CI)	PAF (%)	(95% CI)	PAF (%)	(95% CI)	PAF (%)	(95% CI)	PAF (%)	(95% CI)
Men, 2010										
20–29	0.1	(−0.3, 0.6)	0.5	(0.1, 1.9)	1.1	(0.3, 3.9)	0.5	(0.0, 2.0)	0.7	(0.1, 2.5)
30–39	0.2	(−0.5, 1.1)	1.4	(0.8, 2.3)	3.1	(1.9, 4.6)	1.3	(0.2, 2.9)	1.8	(0.7, 3.3)
40–49	0.5	(−1.5, 3.0)	3.9	(2.2, 6.1)	8.2	(5.5, 11.5)	3.5	(0.5, 7.6)	4.9	(2.0, 8.5)
50–59	0.9	(−2.9, 5.6)	7.3	(4.1, 10.9)	14.5	(10.0, 19.7)	6.6	(1.0, 13.6)	8.9	(3.9, 15)
60–69	1.0	(−3.3, 6.3)	8.1	(4.6, 12.2)	16.1	(11.2, 21.6)	7.4	(1.1, 15)	9.9	(4.4, 16.5)
70+	1.0	(−3.4, 6.5)	8.3	(4.7, 12.5)	16.5	(11.4, 22.2)	7.5	(1.1, 15.4)	10.2	(4.5, 17)
Men, 2030										
20–29	0.0	(−0.3, 0.7)	0.4	(0.1, 2.2)	0.9	(0.2, 4.7)	0.4	(0.0, 2.3)	0.5	(0.1, 2.9)
30–39	0.1	(−0.3, 0.7)	0.9	(0.4, 1.5)	1.8	(1.0, 3.1)	0.8	(0.1, 1.9)	1.1	(0.4, 2.1)
40–49	0.3	(−1.1, 2.3)	2.9	(1.5, 4.7)	6.0	(3.7, 9.1)	2.6	(0.4, 5.8)	3.5	(1.4, 6.6)
50–59	0.8	(−2.5, 4.9)	6.2	(3.4, 9.7)	12.6	(8.4, 17.7)	5.6	(0.8, 11.9)	7.6	(3.2, 13.3)
60–69	1.2	(−4.1, 7.6)	9.7	(5.5, 14.6)	18.9	(13.1, 25.5)	8.8	(1.3, 17.9)	11.8	(5.2, 19.6)
70+	1.4	(−4.8, 8.8)	11.2	(6.3, 16.6)	21.4	(14.9, 28.5)	10.1	(1.5, 20.2)	13.5	(6.0, 22.2)
Women, 2010										
20–29	2.6	(0.1, 15.5)	−0.1	(−0.4, 0.3)	0.6	(0.1, 2.0)	0.3	(−0.1, 1.3)	0.9	(0.2, 3.3)
30–39	4.4	(0.1, 20.5)	−0.1	(−0.5, 0.4)	1.0	(0.3, 2.5)	0.5	(−0.2, 1.8)	1.5	(0.4, 4.1)
40–49	10.6	(0.4, 38.1)	−0.2	(−1.2, 0.9)	2.6	(0.9, 5.3)	1.2	(−0.5, 4.0)	3.9	(1.0, 8.9)
50–59	19.7	(0.8, 55.6)	−0.5	(−2.4, 1.9)	5.3	(1.9, 9.9)	2.4	(−1.0, 7.7)	7.8	(2.1, 16.3)
60–69	27.7	(1.2, 66.0)	−0.8	(−3.7, 3.0)	8.0	(3.0, 14.5)	3.8	(−1.6, 11.5)	11.6	(3.3, 23.1)
70+	31.2	(1.4, 69.7)	−1.0	(−4.4, 3.5)	9.3	(3.5, 16.6)	4.4	(−1.9, 13.3)	13.4	(3.9, 26.1)
Women, 2030										
20–29	2.0	(0.0, 14.7)	0.0	(−0.4, 0.2)	0.5	(0.1, 2.1)	0.2	(−0.1, 1.3)	0.7	(0.1, 3.3)
30–39	2.4	(0.1, 13.2)	−0.1	(−0.3, 0.2)	0.6	(0.2, 1.6)	0.3	(−0.1, 1.1)	0.8	(0.2, 2.7)
40–49	7.5	(0.2, 31.1)	−0.2	(−0.9, 0.7)	1.8	(0.6, 4.2)	0.8	(−0.3, 3.1)	2.7	(0.6, 7.1)
50–59	16.2	(0.6, 50.3)	−0.4	(−1.9, 1.6)	4.2	(1.5, 8.3)	1.9	(−0.8, 6.4)	6.2	(1.6, 13.8)
60–69	28.4	(1.2, 67.2)	−0.8	(−3.9, 3.1)	8.3	(3.1, 15.3)	3.9	(−1.7, 12.1)	12.0	(3.4, 24.2)
70+	30.9	(1.4, 69.5)	−0.9	(−4.4, 3.5)	9.2	(3.5, 16.6)	4.4	(−1.9, 13.3)	13.3	(3.8, 26.1)

†Summary relative risks in the pooled analysis of Japanese cohorts showed a null association between diabetes and oesophagus cancer incidence among men. ‡Summary relative risks in the pooled analysis of Japanese cohorts showed a null association between diabetes and colon and bile duct cancer among women. CI, confidence interval.

and women aged below 60 years showed a marginal decrease across cancer sites, including colon, liver, bile duct, and pancreas. Results from the sensitivity analysis showed that the latency period of 15 years showed no major difference from 10-year and 20-year latency periods, and the 15-year latency period yielded most conservative estimates (Table S1).

Discussion

This study provides the first comprehensive evidence on the current and future burden of cancer associated with type 2 diabetes in the Japanese population. Using the latest data on site-specific cancer incidence, we also estimated the number of excess cancer cases associated with diabetes in 2010 and 2030. Previous studies have investigated the impact of diabetes on the cancer burden.[7,18] Lam *et al.*[7] estimated PAFs for cancer mortality in Japan of 3.7% for pancreatic cancer and 2.4% for liver cancer as of 2009. However, these estimates cannot be directly compared with those of the present study because the outcome was mortality and not the incidence of cancer. Particularly, the difference between the PAF for cancer mortality from Lam's study and the PAF for cancer incidence in our study can be explained by early detection, as diabetic patients receive medical follow-up and have an increased chance of cancer screening, such as screening for pancreatic cancer, in the course of diabetes care.[24] Furthermore, comparison with the results of Lin *et al.*[25] in the Taiwanese population shows that the PAFs for liver and pancreatic cancer were higher in Japan, despite similar diabetes prevalence estimates, the differences being mainly explained by higher relative risk estimates used in our study.[8] We also observed a sex difference in the PAF estimates, particularly with the incidence of oesophageal, colon, and bile duct cancers. Previous studies suggested that etiological differences in progression of diabetes leading to cancer may play a role, probably due to different hormonal environments.[26]

Our prediction showed that the PAF of cancers associated with type 2 diabetes mellitus will modestly increase in men between 2010 and 2030. The increase in PAF values are due to the predicted increase in diabetes prevalence, as the relative risks for the various cancer sites associated with diabetes were assumed to be constant over time in this study. The prevalence of diabetes is expected to increase mainly because of the aging of the Japanese population, which is more pronounced in older men aged 60–69 years (17.8% in 2010 to 21.5% in 2030) and in those 70 years and above (20.1% in 2010 to 27.2% in 2030), but not in people below 60 years.[5] Although the PAF values for women are not expected to change in 20 years, the number of excess attributable cases was predicted to increase due to a rise in the overall incidence of cancer.

With the cancer incidence predicted to increase in 2030 but the mortality shown to decrease in the same period, our results

suggest that people living with cancer may increase over time. Understanding the burden of preventable risk factors on cancer occurrence is thus essential from a public health point of view because it will help to focus cancer prevention strategies on major risk factors. For instance, Inoue *et al.*[27] published the first comprehensive assessment of the cancer burden associated with preventable risk factors in the Japanese population. In their study, tobacco smoking, infections, and alcohol drinking were the three most important preventable risk factors in terms of PAFs for cancer incidence after adjustment of confounders. Our study found that type 2 diabetes accounted for approximately 1.7% of all incident cancer cases in men and 1.0% in women in 2010 (2.2% in men and 1.1% in women in 2030) with confounder adjustment. This means that the impact of type 2 diabetes on total cancer occurrence is smaller than smoking (19.5%), infections (20.6%), and alcohol drinking (6.3%), but are comparable to salt consumption (1.6%) and body mass index (1.1%).[27] Management of shared risk factors for diabetes and cancer, such as physical activity and being overweight, might be beneficial in preventing further increases in cancer incidence.

The major strength of this study lies in its use of the best available evidence from the Japanese population. The RRs of cancer incidence by site were extrapolated from a pooled analysis of Japanese cohorts with more than 330 000 adults,[5] which allowed computation of more realistic estimates of the risks specific to Japanese than would be obtained by borrowing RRs from other populations. The only exception is the PAF of oesophageal cancer: it is derived from the RRs with a limited number of cases and wide confidence intervals, even with the pooled data, and any interpretation of the impact of oesophageal cancer should therefore be made with caution due to the uncertainties. Furthermore, it has been reported that the prevalence of diabetes varies by Western and Asian populations, which will likely be widened by the dynamics of population structure over time.[28] The prevalence estimates used in this study were derived from a meta-regression analysis covering more than 160 000 adults from the latest studies and national surveys in Japan,[8] allowing us to reflect lifestyle and demographic changes of this aging country.

Several limitations of this study warrant mention. First, we used all stages of type 2 diabetes mellitus as a single category. People using glucose-lowering medications such as exogenous insulin had a higher cancer risk than those on metformin in a large retrospective cohort study.[29] However, we were unable to differentiate the types of treatment due to a lack of information on whether the people were at an advanced stage of diabetes with glucose-lowering therapy. Second, the interpretation of PAF is based on the assumption of causality between diabetes and cancer occurrence. Several biological mechanisms have been proposed to explain the development of cancer in those with type 2 diabetes, including hyperglycaemia, hyperinsulinemia, or production of inflammatory cytokines.[30] However, the causal effect of diabetes has not yet been ascertained. In particular, for pancreatic cancer, there is a possibility of reverse causality: in a meta-analysis of 35 cohort studies, Ben *et al.*[9] showed that pancreatic cancer was inversely correlated with the duration of diabetes, suggesting that in a substantial proportion of pancreatic cancer cases, diabetes might be a consequence of cancer progression rather than a cause. Nonetheless, as both diseases share common factors such as lack of physical activity, obesity, and poor diet,[31] it is still important to provide public health policies aimed at those common risk factors in order to decrease the incidence of both diabetes and cancer.

In conclusion, our study shows that the PAF of cancer due to diabetes can be expected to rise between 2010 and 2030, with the increase pronounced in liver, pancreatic, and colon cancer. The prolonged life expectancy in Japan increases the ratio of the elderly population, which may contribute to the overall growth in the prevalence of diabetes and subsequent rise in cancer incidence associated with diabetes.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Table S1. Population attributable fraction of cancer incidence attributable to type 2 diabetes by site of cancer in Japan, 2010 and 2030 using 10- and 20-year latency periods.