Diabetes Mellitus and the Risk of Cancer

Results From a Large-Scale Population-Based Cohort Study in Japan

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Background: An association between diabetes mellitus (DM) and cancer has long been speculated, but no conclusive evidence has been obtained.

Methods: We prospectively examined the association between a history of DM and subsequent risk of cancer in the Japan Public Health Center–Based Prospective Study. A total of 97 771 general Japanese persons (46 548 men and 51 223 women) aged 40 to 69 years who responded to the baseline questionnaire, from January 1990 to December 1994, were followed up for cancer incidence through December 31, 2003. At baseline, 6.7% of men and 3.1% of women had a history of DM.

Results: A total of 6462 cases of newly diagnosed cancer were identified. In men, a 27% increase in the risk of total cancer incidence was observed in those with a history of DM (n=3907 [366 with DM]; hazard ratio [HR], 1.27; 95% confidence interval [CI], 1.14-1.42). The HR was especially high for those with cancer of the liver (n=312 [52 with DM]; HR, 2.24; 95% CI, 1.64-3.04), pancreas (n=118 [16 with DM]; HR, 1.85; 95% CI, 1.07-3.20), and kidney (n=99 [13 with DM]; HR, 1.92; 95% CI, 1.06-3.46). We also observed a moderately increased risk of colon cancer (n=491 [46 with DM]; HR, 1.36; 95% CI, 1.00-1.85) and of stomach cancer with borderline significance (n=977 [87 with DM]; HR, 1.23; 95% CI, 0.98-1.54). In women, a borderline significant increase in risk was observed for the incidence of total cancer (n=2555 [104 with DM]; HR, 1.21; 95% CI, 0.99-1.47), while statistical significance was observed for the incidence of stomach cancer (n=362 [20 with DM]; HR, 1.61; 95% CI, 1.02-2.54) and liver cancer (n=120 [10 with DM]; HR, 1.94; 95% CI, 1.00-3.73) and borderline significance was observed for the incidence of ovarian cancer (n=74 [5 with DM]; HR, 2.42; 95% CI, 0.96-6.09).

Conclusion: Patients with DM drawn from the general Japanese population may be at increased risk of total cancer and of cancer in specific sites.

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THE POSSIBLE ASSOCIATION of diabetes mellitus (DM) with cancer risk has long been speculated, although, to our knowledge, no conclusive evidence has been obtained. This putative association has been investigated mainly by site. Many epidemiologic studies have suggested a positive link between DM and cancer of the liver[1-9] and pancreas.[5-17] Evidence from recent studies and hypothesized mechanisms suggest the possibility of associations with other sites also, including the colon[5-9,18-26] and prostate.[5-9,27-34] Evidence of links with other cancers has been sparse and inconsistent.[5-9,35-41]

As in many other countries, DM is a serious public health problem in Japan. A global estimate projects an increase in prevalence in Japanese persons 20 years and older from 6.5% in 1995 to 8.7% in 2025.[42] In a recent survey,[43] approximately 7.4 million Japanese persons were estimated to have DM in 2002, confirming a remarkable increase in recent years.

The increase in DM will likely influence trends in related health conditions, including cancer. Clarification of the association between DM and cancer in populations with an increasing prevalence, such as Japanese persons, is a crucial task, not only from the causative point of view but also with regard to the formulation of clinical strategies and public health policies for the target population.

Herein, we conducted a cohort analysis on the association between DM and cancer risk using a large-scale population-based study in Japan.

METHODS

STUDY POPULATION

The Japan Public Health Center–Based Prospective Study was launched from January 1990 to December 1994, comprising 11 prefectural

public health center areas. Details of the study design have been provided elsewhere.[44] The study protocol was approved by the institutional review board of the National Cancer Center. In the present analysis, 1 public health center area was excluded because data on cancer incidence were not available.

The study population was defined as all registered Japanese inhabitants in the 10 public health center areas, aged 40 to 69 years at the beginning of each baseline survey. Initially, 133 323 subjects were identified as the study population. After excluding 239 subjects with non-Japanese nationality (n=51), duplicate enrollment (n=4), late report of emigration occurring before the start of follow-up (n=178), and ineligibility because of incorrect birth date (n=6), a population-based cohort of 133 084 subjects was established.

QUESTIONNAIRE

A baseline self-administered questionnaire was conducted from 1990 to 1994, including various lifestyle factors, such as medical history of major diseases, smoking and alcohol drinking status, height and weight, leisure-time physical activity, beverage consumption, and food intake frequency. A total of 106 326 subjects responded to the questionnaire, giving a response rate of 79.9%. Subjects who responded after emigration (n=112) and those with a history of cancer at baseline (n=2219) were excluded from further analysis.

Information on a history of DM in the baseline questionnaire was obtained using the question, "Has a doctor ever told you that you have any of the following diseases?—diabetes mellitus (yes/no)," and was supplemented by another question, "Do you take any anti-diabetic drugs? (yes/no)." History of DM was defined as positive for a response of yes to either question.

FOLLOW-UP

Subjects were followed up from the baseline survey until December 31, 2003. Residence status, including survival, was confirmed through the residential registry. Resident and death registration are required in Japan by law, and the registries are believed to be complete. Inspection of the resident registry is available to anyone under the resident registration law. Among the study subjects, 7879 died, 8197 moved out of the study areas, 4 withdrew their participation, and 228 were lost to follow-up within the follow-up period.

The occurrence of cancer was identified by notification from the major hospitals in the study area and data linkage with population-based cancer registries. Death certificates were used as a supplementary information source. The site and histological features of each case were coded using the *International Classification of Diseases for Oncology, Third Edition*.[45] In our cancer registry system, the proportion of cases for which information was available from death certificates only was 3.7%. For the present analysis, the earliest date of diagnosis was used in cases with multiple primary cancers at different times. A total of 6947 newly diagnosed cancer cases were identified. We excluded 6224 subjects for whom information on a history of DM, cerebrovascular disease or ischemic heart disease, smoking status, alcohol drinking, height and weight, leisure-time physical activity, green vegetable intake, or coffee intake was missing. As a result, 97 771 subjects, including 6462 incident cancer cases, were used for the present analysis.

ANALYSIS

The number of person-years in the follow-up was counted from the date of the baseline survey until the date of occurrence of any cancer, the date of emigration from the study area, the date of death, or the end of the study period, whichever came first. For persons who withdrew from the study or were lost to follow-up, the date of withdrawal and the last confirmed date of presence in the study area, respectively, were used as the date of censor.

The outcome of the study was defined as cancers newly occurring during the study period. Hazard ratios and 95% confidence intervals were used to describe the relative risk of cancer occurrence associated with a history of DM at baseline. The Cox proportional hazards model was used as a control for potential confounding factors, namely, age at baseline (continuous), study area (10 public health center areas), history of cerebrovascular disease (yes or no), history of ischemic heart disease (yes or no), smoking status (0, 1-19, 20-29, 30-39, or ≥40 pack-years), ethanol intake (measured in grams per week, continuous), body mass index (calculated as weight in kilograms divided by the square of height in meters, continuous), leisure-time physical activity (<1 time per month, 1-3 times per month, and ≥1 time per week), green vegetable intake (<3 days per week, 3-4 days per week, and almost every day), and coffee intake (almost never, 1-2 days per week, 3-4 days per week, 1-2 cups per day, 3-4 cups per day, or ≥5 cups per day). These variables, obtained from the questionnaire, are either known or suspected from previous studies as risk factors for cancer. All statistical analyses were performed using Stata, version 9.[46]

RESULTS

During 1 048 474 person-years of follow-up (average follow-up, 10.7 years) for 97 771 subjects (46 548 men and 51 223 women), a total of 6462 cases of newly diagnosed cancer (3907 men and 2555 women) were identified and included in the analyses.

Characteristics of the study subjects are shown in **Table 1**. At baseline, 6.7% of men and 3.1% of women had a history of DM. In both sexes, the proportion of past smokers and nondrinkers was increased in those with a history of DM, and subjects with a history of DM tended to have a higher body mass index but more frequent leisure-time physical activities. The proportion of subjects who almost never drank coffee was higher among those with a history of DM.

In men (**Table 2**), a statistically significant increase in the risk of cancer occurrence was observed in those with a history of DM. The hazard ratio was especially high for cancer of the liver, kidney, and pancreas. We also observed a moderately increased risk of colon cancer with statistical significance and of stomach cancer with borderline significance. The exclusion of liver and pancreatic cancer cases from the analysis for total cancer risk attenuated risk values, but statistical significance was maintained. For cancer of the liver, pancreas, and kidney, estimations of the hazard ratio after the exclusion of those diagnosed as having cancer within 5 years of baseline were similar to those using all cases.

In women (**Table 3**), a borderline significant increase in risk was observed for the incidence of total cancer. Increased risk was observed for stomach and liver cancer, with statistical significance, and for ovarian cancer, with borderline significance.

Table 1. Baseline Characteristics of the 97 771 Study Subjects According to Self-reported History of DM*

Characteristic	Men†			Women‡		
	Total (N = 46 548)	Those Without a History of DM (n = 43 451)	Those With a History of DM (n = 3097)	Total (N = 51 223)	Those Without a History of DM (n = 49 652)	Those With a History of DM (n = 1571)
Age, mean ± SD, y§	51.4 ± 7.9	51.2 ± 7.9	54.0 ± 7.6	51.8 ± 8.0	51.6 ± 8.0	56.0 ± 7.6
Self-reported history of cerebrovascular disease	1.1	1.0	1.7	0.5	0.5	1.3
Self-reported history of ischemic heart disease	1.4	1.3	3.5	0.8	0.7	2.1
Smoking status, pack-years						
0	23.6	23.9	20.6	91.6	91.7	89.4
1-19	18.7	18.9	15.7	5.4	5.4	5.6
20-29	18.1	18.3	15.8	1.3	1.3	2.0
30-39	16.3	16.2	17.4	0.5	0.5	1.5
≥40	23.3	22.7	30.5	1.2	1.1	1.5
Ethanol intake, g/wk						
0	22.5	22.1	27.0	76.9	76.6	84.6
<1	8.9	9.0	8.4	10.1	10.3	6.1
1-149	25.9	26.2	22.7	10.7	10.8	7.2
150-299	21.5	21.8	18.3	1.4	1.4	1.1
300-449	12.8	12.8	13.2	0.5	0.5	0.4
≥450	8.3	8.1	10.4	0.4	0.4	0.6
Body mass index‖						
<18.0	4.3	4.3	4.3	5.9	5.9	4.9
18.0-20.9	14.7	14.7	13.6	16.4	16.5	11.9
21.0-22.9	25.8	25.9	24.2	26.4	26.6	20.2
23.0-24.9	27.9	27.9	27.9	24.0	24.1	21.9
25.0-26.9	16.5	16.4	17.5	14.8	14.6	19.7
27.0-29.9	8.8	8.8	9.6	9.5	9.3	14.5
≥30.0	2.0	2.0	2.9	3.0	3.0	6.9
Leisure-time physical activity						
Almost never	64.9	65.1	62.7	74.7	74.9	69.1
Once per month to 3-4 times per week	15.9	16.1	13.0	7.2	7.3	6.3
Almost every day	19.2	18.8	24.3	18.1	17.9	24.6
Green vegetable intake						
Almost never	14.0	14.0	13.7	9.0	8.9	10.9
1-2 Times per week	29.3	29.4	27.0	23.4	23.5	22.1
3-4 Times per week	33.6	33.7	33.4	37.2	37.3	35.3
Almost every day	23.1	22.9	25.9	30.4	30.3	31.7
Coffee intake						
Almost never	29.8	29.0	40.1	31.5	30.9	52.1
1-2 Times per week	17.7	17.6	19.3	18.3	18.3	17.4
3-4 Times per week	11.6	11.8	9.9	10.8	10.9	7.3
Almost every day						
1-2 Cups per day	26.4	26.8	20.3	29.4	29.8	19.2
3-4 Cups per day	10.8	11.1	7.9	7.9	8.0	3.2
≥5 Cups per day	3.7	3.7	2.5	2.1	2.1	0.8

Abbreviation: DM, diabetes mellitus.
*Data are given as percentage of each group unless otherwise indicated. Percentages may not total 100 because of rounding.
†Those without a history of DM comprised 93.3% of the men; and those with a history of DM, 6.7%.
‡Those without a history of DM comprised 96.9% of the women; and those with a history of DM, 3.1%.
§The age range was 40 to 69 years for all groups.
‖Calculated as weight in kilograms divided by the square of height in meters.

COMMENT

In this prospective cohort study, a past diagnosis of DM was associated with a 27% and a 21% increase in the risk of total cancer incidence in men and women, respectively. The observed risk of total cancer by DM is a "grand sum" of the various impacts of individual sites of cancer. Few studies have clarified the effect of DM on total cancer,[8,9,41] and results have been varied. The present study showed a difference in the magnitude of risk between men and women. Because of the paucity of evidence from previous studies, estimates for total cancer risk from other studies are needed to confirm the validity of our estimate.

By site, the increased risk of liver cancer seen herein is consistent with the risk in previous studies.[1-9] The increased risk of pancreatic cancer, however, was observed only in men, which is inconsistent with the positive association in both sexes suggested in most previous studies.[5-16] We also observed a higher risk in men for colon cancer, while results for women in previous studies

Table 2. Cancer Incidence According to Self-reported History of DM in 46 548 Men*

Site or Type of Cancer	*ICD-O-3* Code	Total No. of Cases	Those Without a History of DM	Those With a History of DM	HR (95% CI) for All Cases		HR (95% CI) Excluding Cases Within 5 y‡
					Adjustment 1†	Adjustment 2‡	
All sites	NA	**3907**	3541	366	1.30 (1.17-1.45)§	1.27 (1.14-1.42)§	1.16 (1.00-1.35)§
All sites excluding the liver	NA	**3595**	3281	314	1.22 (1.09-1.37)§	1.20 (1.06-1.35)§	1.08 (0.92-1.26)
All sites excluding the liver and pancreas	NA	**3477**	3179	298	1.20 (1.06-1.35)§	1.18 (1.04-1.33)§	1.05 (0.89-1.23)
Esophagus	C15	**176**	158	18	1.48 (0.91-2.41)	1.40 (0.84-2.32)	0.96 (0.45-2.09)
Stomach	C16	**977**	890	87	1.22 (0.98-1.52)	1.23 (0.98-1.54)	1.09 (0.79-1.50)
Colon	C18	**491**	445	46	1.40 (1.03-1.90)§	1.36 (1.00-1.85)§	1.14 (0.74-1.75)
Rectum	C19-C21	**243**	228	15	0.85 (0.50-1.43)	0.80 (0.47-1.36)	0.90 (0.46-1.78)
Liver	C22	**312**	260	52	2.37 (1.76-3.20)§	2.24 (1.64-3.04)§	2.30 (1.49-3.55)§
Bile duct	C23-C24	**89**	79	10	1.61 (0.83-3.12)	1.63 (0.84-3.17)	1.89 (0.85-4.21)
Pancreas	C25	**118**	102	16	2.05 (1.20-3.48)§	1.85 (1.07-3.20)§	1.97 (1.01-3.88)§
Larynx	C32	**33**	30	3	1.45 (0.44-4.79)	1.34 (0.40-4.45)	1.74 (0.39-7.66)
Lung	C33-C34	**547**	502	45	1.07 (0.79-1.46)	1.05 (0.77-1.44)	1.00 (0.67-1.50)
Leukemia	C42	**94**	88	6	0.92 (0.40-2.12)	0.99 (0.43-2.28)	1.59 (0.68-3.71)
Prostate	C61	**284**	266	18	0.81 (0.50-1.31)	0.82 (0.51-1.33)	0.50 (0.24-1.01)
Kidney	C64-C66 and C68	**99**	86	13	2.02 (1.13-3.64)§	1.92 (1.06-3.46)§	2.41 (1.22-4.78)§
Bladder	C67	**105**	93	12	1.58 (0.86-2.88)	1.63 (0.89-3.00)	0.82 (0.30-2.27)
Lymphoma	C77	**61**	56	5	1.19 (0.47-2.98)	1.27 (0.50-3.20)	1.01 (0.31-3.29)

Abbreviations: CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; *ICD-O-3*, *International Classification of Diseases for Oncology, Third Edition*; NA, data not applicable.

*The total person-years of follow-up was 488 914.1 (458 724.4 in those without a history of DM and 30 189.7 in those with a history of DM).

†Adjusted for age (in years) at baseline (continuous) and study area (10 public health center areas).

‡Adjusted for age (in years) at baseline (continuous), study area (10 public health center areas), history of cerebrovascular disease, history of ischemic heart disease, smoking (≤19, 20-29, 30-39, or ≥40 pack-years), ethanol intake (in grams per week, continuous), body mass index (continuous), leisure-time physical activity (<1 day per month, 1-3 days per month, or ≥1 day per week), green vegetable intake (<3 days per week, 3-4 days per week, or almost every day), and coffee intake (almost never, 1-2 days per week, 3-4 days per week, 1-2 cups per day, 3-4 cups per day, or ≥5 cups per day).

§These cases showed a significant increase in the risk of cancer occurrence.

Table 3. Cancer Incidence According to Self-reported History of DM in 51 223 Women*

Site or Type of Cancer	*ICD-O-3* Code	Total No. of Cases	Those Without a History of DM	Those With a History of DM	HR (95% CI) for All Cases		HR (95% CI) Excluding Cases Within 5 y‡
					Adjustment 1†	Adjustment 2‡	
All sites	NA	**2555**	2451	104	1.24 (1.01-1.50)§	1.21 (0.99-1.47)	1.23 (0.95-1.59)
All sites excluding the liver	NA	**2435**	2341	94	1.19 (0.96-1.46)	1.16 (0.94-1.43)	1.19 (0.91-1.56)
All sites excluding the liver and pancreas	NA	**2343**	2254	89	1.18 (0.96-1.46)	1.15 (0.93-1.43)	1.19 (0.90-1.56)
Stomach	C16	**362**	342	20	1.58 (1.01-2.49)§	1.61 (1.02-2.54)§	1.92 (1.06-3.47)§
Colon	C18	**303**	293	10	0.93 (0.49-1.75)	0.83 (0.42-1.61)	0.58 (0.21-1.57)
Rectum	C19-C21	**153**	145	8	1.58 (0.77-3.24)	1.65 (0.80-3.39)	1.22 (0.38-3.90)
Liver	C22	**120**	110	10	2.09 (1.09-4.02)§	1.94 (1.00-3.73)§	1.84 (0.79-4.30)
Bile duct	C23-C24	**91**	89	2	0.55 (0.14-2.25)	0.55 (0.13-2.24)	0.57 (0.08-4.14)
Pancreas	C25	**92**	87	5	1.30 (0.53-3.21)	1.33 (0.53-3.31)	1.32 (0.41-4.28)
Lung	C33-C34	**198**	190	8	1.13 (0.56-2.30)	1.12 (0.55-2.29)	1.24 (0.54-2.84)
Leukemia	C42	**80**	76	4	1.45 (0.53-4.00)	1.38 (0.50-3.81)	2.01 (0.61-6.58)
Breast	C50	**451**	441	10	0.84 (0.45-1.57)	0.83 (0.44-1.57)	0.93 (0.44-1.98)
Uterus							
Cervix	C53	**133**	131	2	0.60 (0.15-2.43)	0.61 (0.15-2.48)	0.66 (0.09-4.83)
Corpus	C54	**89**	85	4	1.82 (0.66-4.99)	1.68 (0.61-4.64)	1.30 (0.31-5.38)
Ovary	C56	**74**	69	5	2.49 (0.99-6.23)	2.42 (0.96-6.09)	1.70 (0.41-7.11)
Kidney	C64-C66 and C68	**35**	33	2	1.62 (0.39-6.82)	1.36 (0.32-5.78)	1.44 (0.19-11.14)
Bladder	C67	**30**	29	1	0.82 (0.11-6.07)	0.64 (0.09-4.75)	1.00 (0.13-7.62)
Thyroid	C73	**103**	100	3	1.11 (0.35-3.50)	1.08 (0.34-3.43)	1.74 (0.41-7.29)
Lymphoma	C77	**28**	26	2	2.01 (0.47-8.53)	1.89 (0.43-8.24)	3.03 (0.67-13.73)

Abbreviations: See Table 2.

*The total person-years of follow-up was 559 560.1 (543 313.4 for those without a history of DM and 16 246.7 for those with a history of DM).

†Adjusted for age (in years) at baseline (continuous) and study area (10 public health center areas).

‡Adjusted for age (in years) at baseline (continuous), study area (10 public health center areas), history of cerebrovascular disease, history of ischemic heart disease, smoking (≤19, 20-29, 30-39, or ≥40 pack-years), ethanol intake (in grams per week, continuous), body mass index (continuous), leisure-time physical activity (<1 day per month, 1-3 days per month, or ≥1 day per week), green vegetable intake (<3 days per week, 3-4 days per week, or almost everyday), and coffee intake (almost never, 1-2 days per week, 3-4 days per week, 1-2 cups per day, 3-4 cups per day, or ≥5 cups/day).

§These cases showed a significant increase in the risk of cancer occurrence.

were inconsistent.[19-22,24,25] In contrast, we observed a nonsignificant inverse association between DM and prostate cancer, which is consistent with most previous epidemiologic studies, which showed no[5-9,32] or an inverse[29-31,33,34] association. For other sites, we found a positive association for male kidney and female stomach and ovarian cancers, whereas most previous epidemiologic studies[5-9,38] found no evidence for an association with these cancers, except for a positive association with kidney cancer in diabetic patients[37] and with gastric cancer in *Helicobacter pylori*–positive subjects.[39]

Discussions on the possible biological mechanisms of the association between DM and cancer have tended to be site specific. Notably, however, these associations may be the result of metabolic and hormonal aberrations associated with DM, and common biological mechanisms may be at least partially associated with insulin and insulin-like growth factors (IGFs).[47]

The most obvious change in diabetic patients is reduced insulin sensitivity with compensatory hyperinsulinemia and elevated levels of IGF-1, which may in turn stimulate cell proliferation in the liver, pancreas, colon, prostate, ovary, breast, and other areas.[47-51] At the same time, insulin activates the IGF-1 receptor, which is known to have growth-promoting effects, including modulation of cell cycle progression. Excess insulin might also affect the development of cancer indirectly by downregulating the level of IGF-binding protein 1, which increases the level and bioavailability of total circulating IGF-1. Obesity and physical inactivity also cause hyperinsulinemia and are, thus, also ultimately associated with cancer.[47-51] This seems to be inconsistent with the baseline characteristics of our study population, among whom those with a history of DM tended to have a higher frequency of physical activity at baseline. It is likely that the subjects with a history of DM increased physical activity in response to their condition.

An experimental study[52] revealed that hepatitis C virus infection itself can induce insulin resistance via the action of the hepatitis C virus core protein in disturbing insulin's intracellular signaling pathway. It has also been speculated that *H pylori* gastritis enhances glucose- and meal-stimulated insulin release, probably by increasing gastrin secretion,[53] and that the increased reactive oxygen-related damage to DNA and genetic or epigenetic alterations in gastric mucosa induced by this hyperinsulinemia have a modifying effect on the bacteria, which may be the initial step in the cascade of gastric carcinogenesis.[39] In the present study, hepatitis C virus and *H pylori* infection status were not determined for the entire population, preventing clarification of whether these infections affect the site-specific association between DM and cancer.

Alternatively, the association between DM and cancer could also be considered in combination with the alteration in sex hormone levels occurring in some types of cancer, such as prostate and ovarian cancer. Growth of the prostate gland is controlled by testosterone,[54] and a high testosterone level is associated with prostate cancer.[55] Diabetic men have lower testosterone levels,[56,57] suggesting a decreased risk of prostate cancer. Ovarian tumor development is suggested to be enhanced by androgen, and ovarian androgen excess is related to hyperinsulinemia.[58,59] In contrast, it is also suggested that insulin resistance and chronic hyperinsulinemia induce menstrual cycle irregularity and chronic anovulation, which may reduce the risk of ovarian and breast cancer.[58-60] Because these sex hormone–related mechanisms act in an apparently opposite direction to the hyperinsulinemia and IGF mechanisms previously described, the interpretation of risk values revealed by their combination may be complicated.

Despite the biological plausibility of the association, several issues should be considered when discussing the role of DM as a cause of cancer. First, certain common health conditions are likely to cause DM and cancer. Second, some types of cancer may cause DM as a consequence. Third, it is not easy to differentiate whether DM causes cancer or whether risk factors for DM, such as obesity and physical inactivity, are associated with cancer. Last, it is likely that a diagnosis of DM and subsequent medical care increase vigilance and, thus, the possibility of a diagnosis of cancer. These issues should likely be considered as alternative factors affecting the association between DM and cancer, directly or otherwise.

The major strength of the present study is its prospective design, which avoided exposure recall bias. Other strengths include the following: study subjects were selected from the general population, the response rate of 79.9% to the baseline questionnaire is acceptable for study settings such as this, the proportion of loss to follow-up (0.2%) was negligible, the quality of our cancer registry system was satisfactory during the study period, and potential confounding factors could be adjusted to minimize their influence on risk values. With regard to the last point, however, the possible influence of residual confounding cannot be denied.

Several methodological limitations can also be identified. Assessment of a history of DM was based on self-reports. The questionnaire used for the 5- and 10-year follow-up surveys included similar questions to identify a personal history of DM as those used in the baseline survey, which previously confirmed that 94% of self-reported histories of DM in subjects sampled from our population were consistent with medical records.[61] We considered this to be a sufficiently high positive predictive value for the diagnosis of DM, and not substantially different from the value at baseline. However, the sensitivity and specificity of a past diagnosis of DM for diabetic hyperglycemia from the health checkup data were 46% and 98%, respectively.[61] Furthermore, because information on the use of antidiabetic drugs was used as complementary information, information on insulin injections or calorie restrictions could not be used to complement the primary question. For these reasons, the use of self-reports is likely to underestimate the true prevalence of DM, although such misclassification would bias the association toward the null.

According to a 1988 to 1992 survey in a general population, in which data were derived from self-reports and glycosylated hemoglobin value, the prevalence of DM in subjects 40 years and older was 9.8% in men and 6.8% in women.[62-65] By comparison, the respective baseline rates in our population, of 6.7% and 3.1%, are relatively low,

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probably because our data were based on self-reports only, in which as few as 50% to 60% of cases are detected. This estimate is supported by a subgroup analysis, in which the prevalence of DM estimated by a combination of plasma glucose and glycosylated hemoglobin values was 12.6% in men and 8.6% in women.[66]

The treatment and control of DM may also affect these associations as a result of improvements to hyperglycemia and other lifestyle factors. We could not differentiate the type of DM, although most cases among adults in Japan would be expected to be type 2. The diagnosis of DM after the start of the study may have resulted in the attenuation of the true associations.

Allowing for these methodological issues, our results suggest that a past diagnosis of DM confers an increase in the risk of total cancer incidence of 27% in the Japanese population. The remarkable increase in the diagnosis of DM in Japan in recent years may affect future trends in the incidence and type of cancer.

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