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High hemoglobin A1c levels within the non-diabetic range are associated with the risk of all cancers

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Previous studies have reported associations between diabetes and cancer risk. However, specific association of hemoglobin A1c (HbA1c) levels with cancer risk remains inconclusive. We followed 29,629 individuals (11,336 men; 18,293 women) aged 46–80 years who participated in the Japan Public Health Center-based prospective study who had HbA1c measurements available and were cancer-free at baseline. Cancer incidence was assessed by systemic surveys. We estimated hazard ratios (HRs) for cancer risk with adjustment for age sex, geographic area, body mass index, smoking status, physical activity, alcohol, coffee, vegetable and total energy consumption, and history of cardiovascular disease. After a median follow-up of 8.5 years, 1,955 individuals had developed cancer. Higher HbA1c levels within both the non-diabetic and diabetic ranges in individuals without known diabetes were associated with overall cancer risk. Compared with individuals without known diabetes and HbA1c levels of 5.0–5.4%, the HRs for all cancers were 1.27 (95% confidence interval, 1.07–1.52); 1.01 (0.90–1.14); 1.28 (1.09–1.49); and 1.43 (1.14–1.80) for individuals without known diabetes and HbA1c levels <5.0%, 5.5–5.9%, 6.0–6.4%, and ≥6.5%, respectively, and 1.23 (1.02–1.47) for individuals with known diabetes. The lowest HbA1c group had the highest risk of liver cancer, and HbA1c levels were linearly associated with the risk of all cancers after excluding liver cancer (*P* for linear trend, 0.004). In conclusion, our findings corroborate the notion that glycemic control in individuals with high HbA1c levels may be important not only to prevent diabetes but also to prevent cancer.

Epidemiologic evidence suggests that diabetes is associated with an increased risk of cancer.[1,2] In 2010, the American Diabetes Association and the American Cancer Society jointly published a consensus report on the relationship between diabetes and cancer.[3] The Japan Diabetes Society (JDS) and the Japanese Cancer Association (JCA) have also recently

Key words: hemoglobin A1c, hyperglycemia, diabetes mellitus, cancer incidence

Abbreviations: BMI: body mass index; CI: confidence interval; HbA1c: hemoglobin A1c; HR: hazard ratio; ICD-O-3: International Classification of Diseases for Oncology, Third Edition; JCS: Japanese Cancer Association; JDS: Japan Diabetes Society; JPHC: Japan Public Health Center–based prospective study; P_{linear}: p values for linear trend; $P_{quadratic}$: p values for quadratic trend; PHC: public health center.

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What's new?

Diabetes and cancer share a positive association, yet the relationship between cancer risk and the most reliable blood glucose marker, hemoglobin A1c (HbA1c), remains unclear. This large-scale prospective study with strictly standardized HbA1c values in a Japanese population, which was cancer-free at baseline, shows that elevated HbA1c levels are significantly associated with risk for all reported cancer sites in both sexes, independent of potential confounding factors. The findings support the idea that glycemic control is key to cancer prevention in both diabetic and nondiabetic individuals with high HbA1c levels.

reviewed the existing literature on these diseases and published the JDS/JCA joint committee report on diabetes and cancer[4]. Both reports suggest several underlying mechanisms for the relationship between diabetes and cancer risk, such as hyperglycemia itself, promoting DNA damage through oxidative stress caused by an increased mitochondrial glucose oxidation. Insulin resistance, hyperinsulinemia, elevated levels of free insulin-like growth factor, and chronic inflammation associated with diabetes may also explain the positive association between diabetes and cancer risk.

If hyperglycemia contributes to cancer incidence, glycemic markers are likely correlated with cancer risk in a dose-dependent manner. Previous studies have reported an association between high blood glucose levels and cancer[5,6]. However, the potential association between blood glucose levels and specific cancer sites remains inconclusive. Moreover, the use of blood glucose level as a marker of cancer risk is limited by high intra-individual variability. Alternatively, hemoglobin A1c (HbA1c) level is a reliable glycemic marker as it reflects the 2-month average blood glucose level and exhibits less variability[7]. Therefore, investigating the potential association of HbA1c with cancer risk may provide further insight into the relationship between diabetes and cancer. However, there is little evidence of an association between HbA1c levels and cancer risk,[8–12] particularly in Asians. Most previous studies were relatively small and reported inconsistent results or no significant findings, possibly stemming from insufficient statistical power. Importantly, obesity is an established risk factor for several cancer sites, including the pancreas, colorectum, and post-menopausal breast[13]. Because body fat is strongly associated with HbA1c levels[14], investigating the potential association of HbA1c with cancer risk in a population such as Asians among whom obesity is uncommon may provide greater insight, particularly for cancers that are associated with obesity. However, to the best of our knowledge, no prospective studies have investigated the association of HbA1c levels with overall cancer risk or risk of major cancer sites in an Asian population. One study in Japan evaluated the association between HbA1c and gastric cancer risk in Japan, but the study population was likely too small to evaluate potential association with overall cancer risk or risk at specific cancer sites[15].

Therefore, we conducted a large-scale, population-based, prospective study to determine whether an association exists between HbA1c levels and cancer risk in a general Japanese population free of cancer at baseline.

Materials and Methods

Study population

The Japan Public Health Center-based prospective Study (JPHC Study) was initiated in 1990 (cohort I) and 1993–1994 (cohort II). All subjects were Japanese individuals from 11 public health center (PHC) areas and were aged 40–59 years in 1990 (cohort I) and 40–69 years in 1993 (cohort II), at the time of their first survey. The JPHC Study has been described in detail previously[16]. The JPHC diabetes study, which involved HbA1c measurements and a questionnaire concerning diabetes and lifestyle, was conducted among JPHC Study participants in all PHCs areas except Osaka during routine health check-ups (the first survey was administered in 1998–2000 and the second survey in 2003–2005)[17,18]. Thus, data from the Osaka PHC area were excluded. Another PHC area in Tokyo was excluded because data on cancer incidence were unavailable. Thus, data on the JPHC diabetes study subjects from nine PHC areas who participated in either survey (cohort I: 4 areas; cohort II: 5 areas) were analyzed. Of 35,181 total participants, 1,037 with a history of cancer and 4,515 for whom anthropometric or laboratory data were unavailable were excluded; thus, 29,629 participants were included in the final analysis. All participants provided written informed consent prior to participation in the JPHC diabetes study, and the study was approved by the institutional review boards of the National Cancer Center, Japan, and the National Center for Global Health and Medicine, Japan.

Laboratory assays

HbA1c was measured using high-performance liquid chromatography or immunochemical assays as described elsewhere[17]. In brief, blood samples were collected for HbA1c measurement during the JPHC diabetes study (the first survey conducted from 1998 to 2000 and the second survey conducted from 2003 to 2005). HbA1c values were assayed using high-performance liquid chromatography or immunochemical assays in each public health center laboratory. For calibration, standard samples approved by the Japan Diabetes Society were provided to each laboratory before the surveys, and HbA1c values were strictly calibrated to minimize interlaboratory variation. The overall intra-assay coefficients of variation for HbA1c ranged from 0.0 to 3.4%, and the maximal interassay coefficients of variation ranged from 2.2% to 2.8%. HbA1c values were converted to National Glycohemoglobin Standardization Program values[19]. For individuals who

participated in both surveys of the JPHC diabetes study before the censoring events (~35% of the study population), the average HbA1c level was used for analyses to capture long-term exposure[18,20]. Sensitivity analyses using the time-dependent Cox model to update the HbA1c levels[21] or using the average HbA1c levels weighted by the time intervals between measurements[22] resulted in similar estimates.

Questionnaire survey

Participants completed a self-administered questionnaire at the JPHC Study 5-year and/or 10-year followup that included questions about previously diagnosed medical conditions, medications, and lifestyle factors, including alcohol intake, physical activity, dietary intake, and smoking[16]. Data from the JPHC Study questionnaire administered upon entry into the JPHC diabetes study were used in our analyses, with the exception of data from participants in cohort I who only participated in the second survey. These participants did not complete a JPHC Study questionnaire upon entry into the JPHC diabetes study, and therefore, data from a questionnaire 5 years prior to entry were used in the analysis. Details on the validation of the questionnaire have been described elsewhere[23–27]. In brief, the correlation coefficient estimates for comparison of the questionnaire results with dietary records were: alcohol intake, 0.77 for men and 0.55 for women[23]; vegetable intake, 0.38 for men and 0.44 for women[24,25]; and coffee intake, 0.59 for men and 0.51 for women[26]. Regarding total physical activity, the correlation coefficients between the estimates from the questionnaire and a 4-day, 24-hr physical activity record were 0.53 for men and 0.35 for women[27]. Weight and height were measured during the health check-ups conducted during the JPHC diabetes study. Body mass index (BMI) was calculated in kg/m^2.

Followup

Participants were followed from the time of entry into the JPHC diabetes study until December 31, 2008. Residence status, including survival, was confirmed through the residential registry. In Japan, residency and death registration are required by law, and the registries are considered complete, and thus, accurate. Cancer occurrence was documented through active notifications from the major hospitals in the study areas and data linkage with population-based cancer registries. Death certificates were also used as a supplementary information source. The site and histological features of each cancer case were coded according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3)[28]. For the registry system used, 7.7% of the cases only had information available from death certificates. For analysis, the earliest date of diagnosis was considered for cases with multiple primary cancers occurring at different times.

Statistical analysis

We analyzed data from 29,629 participants aged 46–80 years upon their entry into the JPHC diabetes study. Each participant contributed person-years from the time of entry into the JPHC diabetes study until the censoring event: first cancer event, death, change in residence, loss to follow-up, or December 31, 2008. If individuals participated in both surveys, the time of entry for the first survey was regarded as the starting point. Baseline characteristics were calculated for 6 groups: individuals without known diabetes and HbA1c levels <5.0% (<31 mmol/mol), 5.0–5.4% (32–36 mmol/mol), 5.5–5.9% (37–41 mmol/mol), 6.0–6.4% (42–47 mmol/mol), and ≥6.5% (≥48 mmol/mol), and individuals with diagnosed diabetes. Participants were defined as having "known diabetes" if they self-reported "diabetes" or "treatment for diabetes" in the JPHC diabetes study questionnaire. Following conventional practice, the HbA1c category of 5.0%–5.5% was used as the reference category[18,29]. Cox proportional hazards models were used to examine the cancer risk in each group, and the hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. In Model 1, data were adjusted for age, sex, and PHC area. In Model 2, further adjustments were made for BMI (continuous), smoking status (never smoked, past smoker, or current smoker), sports and physical activity (≥1 day/week, other), alcohol consumption (non-current drinker, occasional drinker, or current drinker in quartiles of ethanol intake in g/week), energy-adjusted vegetable intake (quartiles), total energy intake (quartiles), coffee consumption (almost never, 1–2 cups/week, 3–6 cups/week, 1 cup/day, 2–3 cups/day, or ≥4 cups/day), and history of cardiovascular disease (coronary heart disease or stroke). Further analyses were conducted excluding cancer cases with an early diagnosis (<3 years of follow-up). The physical activity questionnaires administered at the JPHC Study 5- and 10-year follow-up time points differed slightly. Therefore, separate estimates for those who completed questionnaires in the second and third surveys were calculated. Because there was no apparent difference in estimates between these groups, pooled results were computed using a fixed-effects model with inverse variance weighting. For participants without known diabetes, 2-sided P values for linear trends (P_{linear}) were computed by assigning a mean HbA1c value to each category and including the variables as continuous variables in the models. Two-sided P values for quadratic trends ($P_{quadratic}$) were computed by also including a quadratic term in each linear trend model. The scaled Schoenfeld residuals[30] indicated that the proportional hazards assumption had been met. The threshold for significance was set at $P < 0.05$. Analyses were performed using Stata version 13.1 (StataCorp, College Station, TX, USA).

Results

During 226,077 person-years of follow-up (median follow-up: 8.5 years) on 29,629 subjects (11,336 men, 18,293 women), cancer was newly diagnosed in 1,955 individuals (1,139 men, 816 women; incidence rate, overall: 8.6 per 1,000 person-years, men: 13.7, women: 5.7): stomach cancer (ICD-O-3 topology code: C16), 282 cases (incidence rate: 1.2 per 1,000

Table 1. Baseline characteristics according to HbA1c level and diabetes status (N = 29,629).

	HbA1c levels in participants without known diabetes						
	HbA1c <5.0% (<31 mmol/mol)	HbA1c 5.0–5.5% (32–36 mmol/mol)	HbA1c 5.5–6.0% (37–41 mmol/mol)	HbA1c 6.0–6.5% (42–47 mmol/mol)	HbA1c ≥6.5% (≥48 mmol/mol)	*P* for linear trend	Participants with known diabetes
Characteristic[1]	*n* = 2,070	*n* = 8,314	*n* = 12,636	*n* = 3,711	*n* = 1,037		*n* = 1,861
Mean HbA1c (%)	4.8 ± 0.2	5.2 ± 0.1	5.7 ± 0.1	6.1 ± 0.1	7.1 ± 0.9		7.0 ± 1.3
Age (years)	61.7 ± 8.1	62.1 ± 7.3	62.8 ± 6.6	63.4 ± 6.4	63.4 ± 6.5	<0.001	64.2 ± 6.4
Men[2] (%)	43.8	36.8	34.8	39.7	48.7	0.006	51.9
BMI[2] (kg/m^2)	23.4 ± 3.1	23.4 ± 3.1	23.7 ± 3.1	24.3 ± 3.3	25.1 ± 3.6	<0.001	24.3 ± 3.4
Diabetes treatment (%)	NA	NA	NA	NA	NA		64.3
No medication (%)	NA	NA	NA	NA	NA		45.5
Oral hypoglycemic agents only	NA	NA	NA	NA	NA		48.0
Insulin	NA	NA	NA	NA	NA		6.5
Current smoking[2] (%)	14.2	12.9	14.6	18.4	25.3	<0.001	19.1
Past smoking[2] (%)	10.6	10.0	10.7	12.7	13.7	<0.001	16.3
Sports and physical activity ≥1 day(s)/week,[2] (%)	34.6	40.9	46.7	48.2	49.9	<0.001	49.1
Current alcohol consumption,[2,3] (%)	35.8	32.0	30.2	34.5	39.3	0.035	37.0
Ethanol consumption,[2,3] g/week (among current drinkers)	244 (82–404)	171 (81–325)	164 (79–324)	207 (82–333)	242 (122–383)	0.056	226 (101–397)
Vegetable intake,[2,4] (g/day)	192 (127–281)	206 (136–302)	210 (139–312)	207 (132–312)	195(12–286)	0.09	208 (130–310)
Total energy intake,[2] kcal/day	1,873 (1,497–2,409)	1,934 (1,534–2,426)	1,971 (1565–2471)	1,991 (1,598–2,496)	2,031 (1,617–2,536)	<0.001	1,891 (1,510–2,379)
Coffee consumption ≥1 cup/day,[2] (%)	34.5	35.8	34.9	33.9	33.8	0.14	28.2

Data are presented as mean ± standard deviation or median (interquartile range).
Abbreviations: BMI, body mass index; NA, not applicable.
[1]Baseline characteristics were compared among groups using linear regression analysis for continuous variables and logistic regression analysis for categorical variables. Adjustment for age was performed with the exception of HbA1c.
[2]Adjusted for age.
[3]Alcohol consumption at least once per week.
[4]Energy-adjusted vegetable intake using the residual method.

Table 2. Cancer incidence according to HbA1c level and diabetes status in total participants

		HbA1c levels in participants without known diabetes							
		HbA1c <5.0% (<31 mmol/mol)	HbA1c 5.0–5.5% (32–36 mmol/mol)	HbA1c 5.5–6.0% (37–41 mmol/mol)	HbA1c 6.0–6.5% (42–47 mmol/mol)	HbA1c ≥6.5% (≥48 mmol/mol)	*P* for linear trend	*P* for quadratic trend	Participants with known diabetes
		n = 2,070	*n* = 8,314	*n* = 12,636	*n* = 3,711	*n* = 1,037			*n* = 1,861
	Person-years	16,932	67,322	94,608	26,280	7,352			13,584
All cancers	No. of events	166	515	748	278	93			155
	Incidence rate[1]	9.8	7.6	7.9	10.6	12.6			11.4
	Model 1	1.27 (1.06–1.52)	1.00	1.03 (0.91–1.15)	1.30 (1.11–1.52)	1.50 (1.19–1.88)	0.008	0.019	1.23 (1.03–1.48)
	Model 2	1.27 (1.07–1.52)	1.00	1.01 (0.90–1.14)	1.28 (1.09–1.49)	1.43 (1.14–1.80)	0.028	0.021	1.23 (1.02–1.47)
	Model 2 + Excluding early diagnosis cases (≤3 years)	1.13 (0.90–1.41)	1.00	0.98 (0.85–1.13)	1.29 (1.07–1.56)	1.12 (0.82–1.54)	0.26	0.75	1.30 (1.04–1.62)
All cancers excluding liver cancer	No. of events	147	492	724	273	89			144
	Incidence rate[1]	8.7	7.3	7.7	10.4	12.1			10.6
	Model 1	1.18 (0.98–1.42)	1.00	1.04 (0.93–1.17)	1.33 (1.14–1.56)	1.51 (1.20–1.91)	0.001	0.13	1.20 (0.99–1.45)
	Model 2	1.18 (0.98–1.42)	1.00	1.03 (0.91–1.09)	1.31 (1.12–1.54)	1.45 (1.15–1.83)	0.004	0.13	1.20 (0.996–1.46)
Stomach cancer	No. of events	22	78	114	39	11			18
	Incidence rate[1]	1.3	1.2	1.2	1.5	1.5			1.3
	Model 1	1.11 (0.69–1.80)	1.00	0.99 (0.73–1.33)	1.15 (0.77–1.74)	1.09 (0.59–2.06)	0.92	0.70	0.94 (0.55–1.59)
	Model 2	1.09 (0.68–1.77)	1.00	0.96 (0.71–1.29)	1.08 (0.72–1.63)	0.94 (0.49–1.77)	0.72	0.85	0.86 (0.51–1.46)
Colorectal cancer	No. of events	19	83	111	53	18			21
	Incidence rate[1]	1.1	1.2	1.2	2.0	2.4			1.5
	Model 1	0.94 (0.57–1.57)	1.00	0.96 (0.72–1.28)	1.57 (1.10–2.26)	1.76 (1.05–2.97)	0.003	0.57	1.12 (0.69–1.82)
	Model 2	0.95 (0.57–1.58)	1.00	0.95 (0.71–1.27)	1.51 (1.05–2.17)	1.70 (1.001–2.88)	0.009	0.55	1.13 (0.69–1.85)
Colon cancer	No. of events	14	61	78	38	14			16
	Incidence rate[1]	0.8	0.9	0.8	1.4	1.9			1.2
	Model 1	0.93 (0.52–1.68)	1.00	0.92 (0.65–1.30)	1.31 (1.05–2.48)	2.02 (1.12–3.67)	0.006	0.40	1.28 (0.72–2.28)
	Model 2	0.95 (0.52–1.71)	1.00	0.91 (0.64–1.29)	1.55 (1.01–2.40)	1.93 (1.05–3.53)	0.013	0.38	1.31 (0.73–2.35)

Table 2. Cancer incidence according to HbA1c level and diabetes status in total participants (Continued)

		HbA1c levels in participants without known diabetes							
		HbA1c <5.0% (<31 mmol/mol)	HbA1c 5.0–5.5% (32–36 mmol/mol)	HbA1c 5.5–6.0% (37–41 mmol/mol)	HbA1c 6.0–6.5% (42–47 mmol/mol)	HbA1c ≥6.5% (≥48 mmol/mol)	*P* for linear trend	*P* for quadratic trend	Participants with known diabetes
Rectal cancer	No. of events	5	22	33	15	4			5
	Incidence rate[1]	0.3	0.3	0.3	0.6	0.5			0.4
	Model 1	1.01 (0.37–2.78)	1.00	1.04 (0.60–1.79)	1.51 (0.78–2.95)	1.19 (0.40–3.53)	0.25	0.86	0.94 (0.35–2.52)
	Model 2	0.99 (0.36–2.73)	1.00	1.04 (0.60–1.80)	1.42 (0.72–2.79)	1.16 (0.38–3.52)	0.31	0.84	0.97 (0.36–2.61)
Liver cancer	No. of events	19	23	23	6	4			11
	Incidence rate[1]	1.1	0.3	0.2	0.2	0.5			0.8
	Model 1	3.28 (1.77–6.07)	1.00	0.74 (0.41–1.32)	0.70 (0.28–1.72)	1.31 (0.45–3.85)	0.013	< 0.001	1.89 (0.87–4.10)
	Model 2	3.30 (1.77–6.13)	1.00	0.72 (0.40–1.28)	0.63 (0.25–1.55)	1.12 (0.38–3.33)	0.006	< 0.001	1.69 (0.77–3.71)
Pancreatic cancer	No. of events	11	16	34	13	6			10
	Incidence rate[1]	0.6	0.2	0.4	0.5	0.8			0.7
	Model 1	2.61 (1.19–5.73)	1.00	1.69 (0.92–3.10)	2.27 (0.99–5.20)	4.29 (1.47–12.49)	0.064	0.22	2.79 (1.18–6.58)
	Model 2	2.69 (1.22–5.92)	1.00	1.70 (0.92–3.12)	2.29 (0.99–5.28)	4.40 (1.49–13.0)	0.053	0.21	2.84 (1.20–6.75)
Lung cancer	No. of events	27	86	121	41	9			21
	Incidence rate[1]	1.6	1.3	1.3	1.6	1.2			1.5
	Model 1	1.21 (0.78–1.88)	1.00	0.99 (0.75–1.32)	1.14 (0.76–1.71)	0.93 (0.46–1.89)	0.69	0.90	0.99 (0.61–1.59)
	Model 2	1.17 (0.76–1.82)	1.00	0.97 (0.73–1.29)	1.13 (0.75–1.69)	0.90 (0.44–1.84)	0.61	093	1.07 (0.66–1.74)

Data are presented as hazard ratios (95% confidence intervals) unless otherwise indicated.
[1]Crude incidence rate per 1,000 person-years.
Model 1 was adjusted for age, sex, and public health center area.
Model 2 was further adjusted for body mass index (continuous), smoking status (never smoked, past smoker, or current smoker), sports and physical activity (≥1 day/week or other), alcohol consumption (non-current drinker, occasional drinker, or current drinker in quartiles of ethanol intake in g/week), energy-adjusted vegetable intake (quartiles), total energy intake (quartiles), coffee consumption (almost never, 1–2 cups/week, 3–6 cups/week, 1 cup/day, 2–3 cups/day, or ≥ 4 cups/day), and history of cardiovascular disease (coronary heart disease or stroke).

Table 3. Cancer incidence according to HbA1c level and diabetes status in men

		HbA1c levels in participants without known diabetes							
		HbA1c <5.0% (<31 mmol/mol)	HbA1c 5.0–5.5% (32–36 mmol/mol)	HbA1c 5.5–6.0% (37–41 mmol/mol)	HbA1c 6.0–6.5% (42–47 mmol/mol)	HbA1c ≥6.5% (≥48 mmol/mol)	*P* for linear trend	*P* for quadratic trend	Participants with known diabetes
		n = 894	n = 3,038	n = 4,418	n = 1,492	n = 510			*n* = 984
	Person-years	6,968	23,638	31,686	10,282	3,449			6,923
All cancers	No. of events	113	281	407	171	60			107
	Incidence rate[1]	16.2	11.9	12.8	16.6	17.4			15.5
	Model 1	1.43 (1.15–1.79)	1.00	1.09 (0.94–1.28)	1.43 (1.17–1.75)	1.53 (1.15–2.03)	0.021	0.073	1.27 (1.01–1.59)
	Model 2	1.42 (1.14–1.77)	1.00	1.07 (0.92–1.26)	1.39 (1.14–1.70)	1.43 (1.07–1.91)	0.063	0.080	1.25 (0.997–1.58)
	Model 2 + excluding early diagnosis cases (≤3 years)	1.31 (0.99–1.72)	1.00	1.09 (0.90–1.32)	1.50 (1.17–1.93)	1.11 (0.74–1.66)	0.27	0.85	1.35 (1.02–1.79)
All cancers excluding liver cancer	No. of events	100	268	392	167	57			100
	Incidence rate[1]	14.4	11.3	12.4	16.2	16.5			14.4
	Model 1	1.33 (1.05–1.68)	1.00	1.10 (0.94–1.29)	1.47 (1.20–1.80)	1.54 (1.14–2.06)	0.006	0.28	1.24 (0.98–1.57)
	Model 2	1.31 (1.04–1.66)	1.00	1.08 (0.93–1.27)	1.43 (1.16–1.75)	1.45 (1.07–1.95)	0.019	0.29	1.24 (0.98–1.57)
Stomach cancer	No. of events	17	45	67	29	7			12
	Incidence rate[1]	2.4	1.9	2.8	2.0	2.0			1.7
	Model 1	1.27 (0.72–2.22)	1.00	1.10 (0.74–1.63)	1.54 (0.92–2.58)	1.11 (0.50–2.47)	0.63	0.93	0.92 (0.48–1.77)
	Model 2	1.22 (0.69–2.14)	1.00	1.08 (0.73–1.60)	1.44 (0.86–2.42)	0.93 (0.41–2.09)	0.97	0.72	0.81 (0.42–1.57)
Colorectal cancer	No. of events	12	37	51	24	12			14
	Incidence rate[1]	1.7	1.6	1.6	2.3	3.5			2.0
	Model 1	1.39 (0.69–2.81)	1.00	1.00 (0.65–1.53)	1.49 (0.89–2.51)	1.95 (0.99–3.82)	0.027	0.26	1.21 (0.64–2.26)
	Model 2	1.33 (0.66–2.70)	1.00	1.00 (0.65–1.53)	1.45 (0.86–2.46)	1.85 (0.93–3.70)	0.043	0.30	1.19 (0.63–2.24)
Liver cancer	No. of events	13	13	15	4	3			7
	Incidence rate[1]	1.9	0.6	0.5	0.4	0.9			1.0
	Model 1	3.73 (1.72–8.08)	1.00	0.93 (0.44–1.96)	0.87 (0.28–2.69)	1.61 (0.45–5.70)	0.11	0.002	1.78 (0.65–4.86)
	Model 2	3.96 (1.80–8.73)	1.00	0.93 (0.44–1.96)	0.79 (0.25–2.46)	1.29 (0.36–4.70)	0.074	0.002	1.74 (0.63–4.85)

Table 3. Cancer incidence according to HbA1c level and diabetes status in men (Continued)

		HbA1c levels in participants without known diabetes							
		HbA1c <5.0% (<31 mmol/mol)	HbA1c 5.0–5.5% (32–36 mmol/mol)	HbA1c 5.5–6.0% (37–41 mmol/mol)	HbA1c 6.0–6.5% (42–47 mmol/mol)	HbA1c ≥6.5% (≥48 mmol/mol)	*P* for linear trend	*P* for quadratic trend	Participants with known diabetes
Prostate cancer	No. of events	22	76	90	35	10			21
	Incidence rate[1]	3.2	3.2	2.8	3.4	2.9			3.0
	Model 1	1.07 (0.66–1.72)	1.00	0.84 (0.61–1.15)	1.05 (0.69–1.60)	1.13 (0.56–2.26)	0.65	0.72	0.90 (0.55–1.46)
	Model 2	1.08 (0.67–1.75)	1.00	0.86 (0.62–1.18)	1.07 (0.70–1.63)	1.20 (0.60–2.42)	0.76	0.70	0.93 (0.57–1.53)

Data are presented as hazard ratios (95% confidence intervals) unless otherwise indicated.
[1]Crude incidence rate per 1,000 person-years.
Model 1 was adjusted for age and public health center area.
Model 2 was further adjusted for body mass index (continuous), smoking status (never smoked, past smoker, or current smoker), sports and physical activity (≥1 day/week or other), alcohol consumption (non-current drinker, occasional drinker, or current drinker in quartiles of ethanol intake in g/week), energy-adjusted vegetable intake (quartiles), total energy intake (quartiles), coffee consumption (almost never, 1–2 cups/week, 3–6 cups/week, 1 cup/day, 2–3 cups/day, or ≥4 cups/day), and history of cardiovascular disease (coronary heart disease or stroke).

person-years); colon cancer (C18), 221 cases (incidence rate: 1.0 per 1,000 person-years); rectal cancer (C19 to C21), 84 cases (incidence rate: 0.4 per 1,000 person-years); liver cancer (C22), 86 cases (incidence rate: 0.4 per 1,000 person-years); pancreatic cancer (C25), 90 cases (incidence rate: 0.4 per 1,000 person-years); lung cancer (C33 to C34), 305 cases (incidence rate: 1.3 per 1,000 person-years); breast cancer (C50), 123 cases (incidence rate, women: 0.9 per 1,000 person-years); prostate cancer (C61), 254 cases (incidence rate, men: 3.1 per 1,000 person-years); other sites, 510 cases (incidence rate, 2.3 per 1,000 person-years). During follow-up, 835 individuals (2.8%) died, 416 (1.4%) moved away from the study areas, and 31 (0.1%) were lost to follow-up.

Compared with participants with lower HbA1c levels, those with higher levels of HbA1c tended to be older, male, current or past smokers, have higher BMI, have higher energy consumption, be engaged in physical activity, and have lower coffee consumption (Table 1; $P_{linear} < 0.05$).

For individuals without known diabetes, those with higher HbA1c levels (within both the non-diabetic and diabetic ranges) had a higher risk of all cancers than those with HbA1c levels of 5.0 to 5.4% (Table 2). Low HbA1c levels (<5.0%) were associated with an increased risk of all cancers (Model 2; $P_{quadratic}$, 0.021). When cancer cases with an early diagnosis (<3 years of follow-up) were excluded, the association for HbA1c levels ≥6.5% and <5.0% was weakened. When cases with liver cancer were excluded, HbA1c levels were linearly associated with overall cancer risk (Model 2; $P_{linear} = 0.004$). Low HbA1c levels were strongly associated with the risk of liver cancer (Model 2; $P_{quadratic} < 0.001$). Higher HbA1c levels (within both the non-diabetic and diabetic ranges) were associated with the risk of colorectal cancer (Model 2; $P_{linear} = 0.009$), especially for colon cancer. In addition, the lowest and highest HbA1c categories were associated with an increased risk of pancreatic cancer, although the wide CIs and non-significant *P* values suggested that the estimates were potentially unstable (Model 2). Known diabetes was associated with an increased risk of all cancers; this association was strengthened slightly when cases of early diagnosis were excluded (Model 2). Known diabetes was also associated with an increased risk of pancreatic cancer (Model 2).

In men, similar patterns of association between HbA1c levels and the risk of all cancers were observed (Table 3). HbA1c levels were not associated with the risk of overall (Table 3), organ-localized, or advanced prostate cancer[31] (data not shown). Women with HbA1c ≥6.5% had higher risks of all cancers and breast cancer (Table 4; Model 2). Further adjustment for menopausal status produced similar findings (data not shown).

Discussion

This study demonstrated that higher HbA1c levels within both the diabetic (≥6.5%) and non-diabetic (6.0–6.4%) ranges were independently associated with the risk of all cancers. Higher HbA1c levels within the non-diabetic range were

Table 4. Cancer incidence according to HbA1c level and diabetes status in women

		HbA1c levels in participants without known diabetes							
		HbA1c <5.0% (<31 mmol/mol)	HbA1c 5.0–5.5% (32–36 mmol/mol)	HbA1c 5.5–6.0% (37–41 mmol/mol)	HbA1c 6.0–6.5% (42–47 mmol/mol)	HbA1c ≥6.5% (≥48 mmol/mol)	*P* for linear trend	*P* for quadratic trend	Participants with known diabetes
		n = 1,176	*n* = 5,276	*n* = 8,218	n = 2,219	*n* = 527			*n* = 877
	Person-years	9,964	43,686	62,922	15,997	3,903			6,661
All cancers	No. of events	53	234	340	108	33			48
	Incidence rate[1]	5.3	5.4	5.4	6.8	8.5			7.2
	Model 1	1.05 (0.78–1.42)	1.00	0.96 (0.81–1.14)	1.16 (0.91–1.48)	1.53 (1.05–2.22)	0.12	0.14	1.23 (0.9–1.68)
	Model 2	1.06 (0.79–1.44)	1.00	0.94 (0.79–1.12)	1.14 (0.89–1.46)	1.50 (1.02–2.18)	0.20	0.12	1.23 (0.89–1.68)
	Model 2 + excluding early diagnosis cases (≤3 years)	0.87 (0.60–1.28)	1.00	0.86 (0.70–1.06)	1.03 (0.76–1.40)	1.24 (0.76–2.02)	0.60	0.40	1.29 (0.89–1.87)
All cancers excluding liver cancer	No. of events	47	224	332	106	32			44
	Incidence rate[1]	4.7	5.1	5.3	6.6	8.2			6.6
	Model 1	0.97 (0.71–1.34)	1.00	0.98 (0.82–1.17)	1.20 (0.93–1.53)	1.55 (1.06–2.26)	0.051	0.29	1.18 (0.85–1.63)
	Model 2	0.99 (0.72–1.36)	1.00	0.97 (0.81–1.15)	1.18 (0.92–1.51)	1.53 (1.04–2.25)	0.080	0.25	1.19 (0.86–1.65)
Stomach cancer	No. of events	5	33	47	10	4			6
	Incidence rate[1]	0.5	0.8	0.7	0.6	1.0			0.9
	Model 1	0.82 (0.32–2.11)	1.00	0.83 (0.53–1.32)	0.65 (0.31–1.36)	1.17 (0.41–3.33)	0.65	0.49	1.07 (0.44–2.62)
	Model 2	0.84 (0.32–2.17)	1.00	0.82 (0.52–1.29)	0.62 (0.30–1.31)	1.06 (0.37–3.06)	0.53	0.48	1.06 (0.43–2.62)
Colorectal cancer	No. of events	7	46	60	29	6			7
	Incidence rate[1]	0.7	1.1	1.0	1.8	1.5			1.1
	Model 1	0.66 (0.30–1.47)	1.00	0.92 (0.61–1.38)	1.78 (1.05–3.01)	1.59 (0.68–3.75)	0.048	0.91	0.96 (0.43–2.14)
	Model 2	0.68 (0.30–1.51)	1.00	0.92 (0.61–1.38)	1.68 (0.99–2.88)	1.56 (0.65–3.72)	0.076	0.97	1.02 (0.46–2.29)
Liver cancer	No. of events	6	10	8	2	1			4
	Incidence rate[1]	0.6	0.2	0.1	0.1	0.3			0.6
	Model 1	2.78 (0.98–7.91)	1.00	0.53 (0.21–1.36)	0.51 (0.11–2.35)	1.80 (0.20–16.4)	0.0498	0.0448	2.30 (0.67–7.87)
	Model 2	2.75 (0.96–7.91)	1.00	0.46 (0.18–1.18)	0.43 (0.09–2.02)	1.67 (0.18–15.7)	0.030	0.054	1.88 (0.54–6.57)

Table 4. Cancer incidence according to HbA1c level and diabetes status in women (Continued)

		HbA1c levels in participants without known diabetes						
		HbA1c <5.0% (<31 mmol/mol)	HbA1c 5.0–5.5% (32–36 mmol/mol)	HbA1c 5.5–6.0% (37–41 mmol/mol)	HbA1c 6.0–6.5% (42–47 mmol/mol)	HbA1c ≥6.5% (≥48 mmol/mol)	*P* for linear trend	*P* for quadratic trend	Participants with known diabetes
Breast cancer	No. of events	7	29	59	14	8			5
	Incidence rate[1]	0.7	0.7	0.9	0.9	2.0			0.8
	Model 1	1.22 (0.53–2.83)	1.00	1.33 (0.83–2.14)	1.37 (0.70–2.69)	3.28 (1.41–7.63)	0.034	0.39	1.18 (0.45–3.07)
	Model 2	1.25 (0.54–2.91)	1.00	1.26 (0.79–2.04)	1.23 (0.63–2.41)	2.83 (1.20–6.68)	0.10	0.43	1.09 (0.42–2.86)

Data are presented as hazard ratios (95% confidence intervals) unless otherwise indicated.
[1]Crude incidence rate per 1,000 person-years.
Model 1 was adjusted for age and public health center area.
Model 2 was further adjusted for body mass index (continuous), smoking status (never smoked, past smoker, or current smoker), sports and physical activity (≥1 day/week, other), alcohol consumption (non-current drinker, occasional drinker, or current drinker in quartiles of ethanol intake in g/week), energy-adjusted vegetable intake (quartiles), total energy intake (quartiles), coffee consumption (almost never, 1–2 cups/week, 3–6 cups/week, 1 cup per day, 2–3 cups/day, or ≥4 cups/day), and a history of cardiovascular disease (coronary heart disease or stroke).

associated with 28% and 51% higher risks of all cancers and of colorectal cancer, respectively. Further, low HbA1c levels were associated with an increased risk of liver cancer. To our knowledge, this study is the first to demonstrate that higher HbA1c levels within both non-diabetic and diabetic ranges in individuals without known diabetes are associated with the risk of all cancers. Our findings provide evidence supporting the notion that glycemic control through lifestyle changes in people with high HbA1c levels may be important not only to prevent diabetes, but also to prevent cancer.

Our findings suggest that hyperglycemia is associated with cancer risk. Only a few studies have evaluated the potential association between HbA1c levels and the risk of all cancers[12,32]. In a New Zealand linkage study with 46,575 participants (mainly Māori) and a relatively short follow-up period of 4.4 years, individuals with HbA1c levels from 6.0 to 6.9% had a 40% higher risk of all cancers than individuals with HbA1c levels <6.0% after adjusting for age, sex, and ethnicity[12]. However, the study lacked anthropometric, physical activity, and dietary data, raising the possibility of residual confounding. In our study, adjusting for a series of potential confounding factors only slightly changed the magnitude of the association for all cancers, suggesting minimal confounding due to traditional cancer risk factors. In the Atherosclerosis Risk in Communities Study of 12,792 participants (mainly European-Americans), compared with non-diabetic individuals with HbA1c levels from 5.0 to 5.6%, only women with HbA1c levels ≥5.7% had a significantly higher risk of all cancers after adjusting for confounding factors (such as age, ethnicity, smoking and BMI). In contrast, we observed a significant association between higher HbA1c levels and the risk of all cancers in both sexes. This discrepancy may be due to the differing effects of glycemia on the risk of all cancers between ethnicities, with a potentially greater impact among Asians than Europeans. Therefore, further studies such as pooled analyses are warranted to clarify ethnic variations in this association.

The fact that the magnitude of the association did not change substantially after adjusting for potential confounding factors suggests that hyperglycemia itself may be important for cancer development. Further, the magnitude of the association between HbA1c levels from 6.0% to 6.4% and the risk of all cancers did not decrease after excluding cancer cases with an early diagnosis. This finding suggests that reverse causality might not explain the higher cancer incidence observed in this category. Higher HbA1c levels within the non-diabetic range (6.0–6.4%) were associated with a 51% higher colorectal cancer risk in our study. Examining the association separately for the colon and rectum showed that individuals with higher HbA1c levels (6.0–6.4% or ≥6.5%) had an increased risk of colon cancer but not rectal cancer. Although earlier published studies evaluated the association between HbA1c levels and the risk of colorectal, colon, or rectal cancer[11,12,32,33], they were limited by relatively small sample sizes or case numbers. A recent meta-analysis

suggests a possible positive association between HbA1c and colorectal cancer; however, the risk for individuals with HbA1c levels in the non-diabetic range was unclear[34]. Thus, our significant findings corroborate the notion that hyperglycemia within the non-diabetic range is associated with an increased risk of colorectal cancer.

The lowest and highest HbA1c categories were also associated with an increased risk of pancreatic cancer. The observed association of the highest HbA1c category with pancreatic cancer risk is consistent with earlier studies showing a strong diabetes–pancreatic cancer risk linkage[1,2]. However, it is uncertain why low HbA1c levels were associated with an increased risk of pancreatic cancer. Low HbA1c levels may be a general marker of poor health[35]. Alternatively, because the CIs were very wide, the observed increased risk could be a chance finding. In contrast to earlier studies in Japan showing no association between diabetes and breast cancer risk[1,2], we observed an increased breast cancer risk for individuals in the highest HbA1c category. Of note, individuals with HbA1c levels <5.0% had a significantly increased risk of liver cancer. Low HbA1c levels may be due to low blood glucose levels or abnormal red blood cell turnover[36]. As an impaired hepatic function can lead to reduced red cell turnover through hypersplenism, such patients have lower HbA1c levels relative to their blood glucose levels[37,38]. This mechanism may partially explain the relationship between low HbA1c levels and liver cancer. In Japan, up to 70% of liver cancer cases are associated with hepatitis C virus infection; however, among the sub-sample of study participants who had data on hepatitis C antibody detection (~30% of participants), a similar pattern of association was found regardless of infection status, indicating that hepatitis C infection may not explain this association between HbA1c level and liver cancer. The previously mentioned New Zealand study reported no association between HbA1c levels and liver cancer risk, possibly because of the small number of liver cancer cases in their cohort ($n = 22$)[12]. Although a previous study in Japan reported a positive association between HbA1c levels and gastric cancer risk, we did not observe such an association[15].Because our population had a high prevalence of *Helicobacter pylori* (~90% of the JPHC participants)[39] and most individuals were already at high risk of developing gastric cancer, hyperglycemia may have only had a limited impact on the development of gastric cancer in our study population[40].

This study's strengths include its population-based prospective cohort design, large sample size, large number of cancer cases, low rate of lost to follow-up, use of standardized HbA1c values, and use of systematic surveys of cancer incidence. Nevertheless, several limitations merit consideration. First, residual confounding may explain some of the observed associations, because individuals with high HbA1c levels within the non-diabetic range tend to have various characteristics that are established risk factors for both hyperglycemia and cancer. For example, we adjusted for self-reported smoking status, but the misclassification of smoking status may have resulted in incomplete control for smoking as a confounding factor. Moreover, information on abdominal obesity was lacking, which may have resulted in incomplete adjustment for adiposity. Second, because of the small numbers of cases, we could not evaluate associations of HbA1c levels with cancers at sites such as the esophagus, kidneys, and uterus; or sex-specific associations for pancreatic and lung cancer. Finally, HbA1c levels and diabetes status may have changed during follow-up. However, if HbA1c levels during follow-up had been available for all participants, the association between HbA1c and cancer risk may have been stronger.

In conclusion, higher HbA1c levels within both non-diabetic and diabetic ranges in Japanese individuals without known diabetes are associated with the risk of all cancers. Since randomized controlled trials have demonstrated that lifestyle changes in people with prediabetes could decrease the risk of type 2 diabetes[41–44], strategies to prevent type 2 diabetes through lifestyle changes have been widely implemented[45]. Our findings suggest that these efforts may also contribute to reduce the incidence of cancer, providing additional strong support for policy makers to implement such diabetes prevention programs.

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APPENDIX

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