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 published a consensus report on the relationship between diabetes and cancer.4 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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Grant sponsor: Ministry of Health, Labour and Welfare of Japan; Grant number: Research on Health Services H10-074; Medical Frontier Strategy Research; H13-008; Clinical Research for Evidence-based Medicine H14-008 and H15-006; Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus H16-019, H17-019, H18-028, H19-016, and H25-016; Grants-in-Aid for Cancer Research and for the Third Term Comprehensive Control Research for Cancer

DOI: 10.1002/ijc.29917

History: Received 16 Aug 2015; Accepted 26 Oct 2015; Online 6 Nov 2015

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reviewed the existing literature on these diseases and published the JDS/JCA joint committee report on diabetes and cancer. 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. 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. 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, 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. Because body fat is strongly associated with HbA1c levels, 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.

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.

### 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.

### 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. 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). 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 immunochromatographic assays as described elsewhere. 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 immunochromatographic 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.
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. Sensitivity analyses using the time-dependent Cox model to update the HbA1c levels or using the average HbA1c levels weighted by the time intervals between measurements 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. 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. 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; vegetable intake, 0.38 for men and 0.44 for women; and coffee intake, 0.59 for men and 0.51 for women. 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. Weight and height were measured during the health check-ups conducted during the JPHC diabetes study. Body mass index (BMI) was calculated in kg/m².

**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). 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. 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 (Plinear) 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 (Pquadratic) were computed by also including a quadratic term in each linear trend model. The scaled Schoenfeld residuals 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 (StatCorp, 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 | Characteristic | Participants with known diabetes | Participants with known diabetes |
|--------------------------------------------------|----------------|---------------------------------|---------------------------------|
| HbA1c < 5.0% (≤31 mmol/mol)                      | n = 2,070      | 64.3                            | 45.5                            |
| HbA1c 5.0–5.5% (32–36 mmol/mol)                  | n = 8,314      |                                |                                 |
| HbA1c 5.5–6.0% (37–41 mmol/mol)                  | n = 12,636     |                                |                                 |
| HbA1c 6.0–6.5% (42–47 mmol/mol)                  | n = 3,711      |                                |                                 |
| HbA1c ≥ 6.5% (≥48 mmol/mol)                      | n = 1,037      |                                |                                 |
| **Mean HbA1c (%)**                               | 4.8 ± 0.2      |                                |                                 |
| **Age (years)**                                  | 61.7 ± 8.1     |                                |                                 |
| **BMI (kg/m²)**                                   | 23.4 ± 3.1     |                                |                                 |
| **Diabetes treatment (%)**                        | NA             |                                |                                 |
| **Oral hypoglycemic agents only (%)**            | NA             |                                |                                 |
| **Insulin (%)**                                   | NA             |                                |                                 |
| **Current smoking (%)**                          | 14.2           |                                |                                 |
| **Past smoking (%)**                             | 10.6           |                                |                                 |
| **Sports and physical activity ≥ 1 day(s)/week (%)** | 34.6          |                                |                                 |
| **Current alcohol consumption (%)**              | 35.8           |                                |                                 |
| **Ethanol consumption (%)**                      | 244 (82–404)   |                                |                                 |
| **Vegetable intake (%)**                         | 192 (127–281)  |                                |                                 |
| **Total energy intake (kcal/day)**               | 1,873 (1,497–2,409) |                        |                                 |
| **Coffee consumption (%)**                       | 34.5           |                                |                                 |

Data are presented as mean ± standard deviation or median (interquartile range).  
Abbreviations: BMI, body mass index; NA, not applicable.  
1Baseline 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.  
2Adjusted for age.  
3Alcohol consumption at least once per week.  
4Energy-adjusted vegetable intake using the residual method.
| 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                  | 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                       |
| 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                       |
| Model 2 +                | Excluding early diagnosis       |                                 |                                  |                             |                 |                 |                             |
|                          | cases (≤3 years)                |                                 |                                  |                             |                 |                 |                             |
| All cancers excluding liver cancer | No. of events | 147                             | 492                              | 724                         | 273             | 89              | 144                         |
|                           | Incidence rate                  | 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                       |
| Model 2                   |                                 | 1.18 (0.98–1.42)                | 1.00                             | 1.03 (0.91–1.10)            | 1.31 (1.12–1.54)| 1.45 (1.15–1.83)| 0.004                       |
| Stomach cancer            | No. of events                   | 22                              | 78                               | 114                         | 39              | 11              | 18                          |
|                           | Incidence rate                  | 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                        |
| 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                        |
| Colorectal cancer         | No. of events                   | 19                              | 83                               | 111                         | 53              | 18              | 21                          |
|                           | Incidence rate                  | 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                       |
| 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                       |
| Colon cancer              | No. of events                   | 14                              | 61                               | 78                          | 38              | 14              | 16                          |
|                           | Incidence rate                  | 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                       |
| 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                       |

**Tumor Markers and Signatures**
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%   | HbA1c 5.5–6.0%   | HbA1c 6.0–6.5%   |
|                  | (32–36 mmol/mol)                                  | (37–41 mmol/mol) | (42–47 mmol/mol) | (≥48 mmol/mol)   |
|                  | P for linear trend                                | P for quadratic  | Participants     |
|                  |                                                   | trend            | with known       |
|                  |                                                   |                  | diabetes         |
| Rectal cancer    | No. of events                                     |                  |                  |                  |
|                  | 5                                                 | 22               | 33               | 15               | 4                | 5                |
|                  | Incidence rate<sup>1</sup>                        |                  |                  |                  |                  |                  |
|                  | 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   |
|                  | 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   |
| Liver cancer     | No. of events                                     |                  |                  |                  |                  |                  |
|                  | 19                                                | 23               | 23               | 6                | 4                | 11               |
|                  | Incidence rate<sup>1</sup>                        |                  |                  |                  |                  |                  |
|                  | 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 |
|                  | 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 |
| Pancreatic cancer| No. of events                                     |                  |                  |                  |                  |                  |
|                  | 11                                                | 16               | 34               | 13               | 6                | 10               |
|                  | Incidence rate<sup>1</sup>                        |                  |                  |                  |                  |                  |
|                  | 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 |
|                  | 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 |
| Lung cancer      | No. of events                                     |                  |                  |                  |                  |                  |
|                  | 27                                                | 86               | 121              | 41               | 9                | 21               |
|                  | Incidence rate<sup>1</sup>                        |                  |                  |                  |                  |                  |
|                  | 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   |
|                  | 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 0.93 1.07   |

Data are presented as hazard ratios (95% confidence intervals) unless otherwise indicated.

<sup>1</sup>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).
| 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 rate1 | 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 rate1 | 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 rate1 | 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 rate1 | 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 rate1 | 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 level | Participants with known diabetes | Participants with non-known diabetes | P for linear trend | P for quadratic trend |
|-------------|---------------------------------|--------------------------------------|-------------------|----------------------|
| <5.0%       | 22                              | 76                                   | 3.2               | 3.2                  |
| 5.0–5.5%    | 90                              | 35                                   | 2.8               | 2.8                  |
| 5.5–6.0%    | 10                              | 10                                   | 3.4               | 3.4                  |
| 6.0–6.5%    | 10                              | 10                                   | 2.9               | 2.9                  |
| 6.5%        | 10                              | 10                                   | 2.9               | 2.9                  |

Data are presented as hazard ratios (95% confidence intervals) unless otherwise indicated.

- **Prostate cancer**
  - No. of events: 22, 76, 90, 35, 10, 21
  - Incidence rate: 3.2, 3.2, 2.8, 3.4, 2.9, 2.9
  - Model 1: 1.07 (0.66–1.72) to 1.08 (0.67–1.75)
  - Model 2: 1.08 (0.67–1.75) to 1.08 (0.67–1.75)

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; $P_{\text{quadratic}} = 0.021$). 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.

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 (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 levels in participants with 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 | 53 | 234 | 340 | 108 | 33 | 48 |
| Incidence rate¹ | 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 | 47 | 224 | 332 | 106 | 32 | 44 |
| Incidence rate¹ | 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 | 5 | 33 | 47 | 10 | 4 | 6 |
| Incidence rate¹ | 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 | 7 | 46 | 60 | 29 | 6 | 7 |
| Incidence rate¹ | 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 | 6 | 10 | 8 | 2 | 1 | 4 |
| Incidence rate¹ | 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 | Participants with known diabetes |
|--------------------------------------------------|---------------------------------|
| HbA1c <5.0% (<31 mmol/mol) | No. of events | Incidence rate<sup>1</sup> | P for linear trend | P for quadratic trend |
| HbA1c 5.0–5.5% (32–36 mmol/mol) | 7 | 0.7 | 0.7 | 0.9 | 0.9 | 2.0 | 0.8 |
| HbA1c 5.5–6.0% (37–41 mmol/mol) | 29 | 1.00 | 1.33 (0.83–2.14) | 0.034 | 0.93 | 1.18 (0.45–3.07) |
| HbA1c 6.0–6.5% (42–47 mmol/mol) | 59 | 1.37 (0.70–2.69) | 1.37 (0.70–2.69) | 3.28 (1.41–7.63) | 0.034 | 0.39 |
| HbA1c ≥6.5% (≥48 mmol/mol) | 14 | 2.0 | 2.83 (1.20–6.68) | 0.10 | 0.43 |
| | 8 | 1.09 (0.42–2.86) | |

Data are presented as hazard ratios (95% confidence intervals) unless otherwise indicated.

<sup>1</sup>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).
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. 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. 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. 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, 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. 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. 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. Although a previous study in Japan reported a positive association between HbA1c levels and gastric cancer risk, we did not observe such an association. Because our population had a high prevalence of *Helicobacter pylori* (~90% of the JPHC participants) 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.

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, strategies to prevent type 2 diabetes through lifestyle changes have been widely implemented. 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.

Acknowledgements

The authors thank all the staff members in each study area for their cooperation and technical assistance to conduct the survey and follow-up. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the results.

APPENDIX

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