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Increased cancer mortality among Japanese individuals with hyperinsulinemia

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ABSTRACT

Aims: To evaluate the effect of hyperinsulinemia on cancer death, we clarified the association between hyperinsulinemia and cancer mortality among Japanese individuals.
Methods: All the participants (5586 men and 6652 women) lived in Hiroshima City, underwent a 75 g oral glucose tolerance test between 1994 and 2012, and were followed for mortality until August 2013. A systematic review of death certificates was used to confirm the cause of death.
Results: During the follow-up period (median, 10.0 years), 587 participants died of cancer. Lung cancer was the most common cause of organ-specific death. We divided the participants into 3 groups according to the tertiles of fasting immunoreactive insulin (FIRI) levels (low, middle, and high groups). The high group had the highest mortality rate (5.5 per 1000 person-years). The hazard ratio (HR) for cancer mortality of the high group after adjustment for possible confounders, such as age, sex, body mass index, smoking status, alcohol intake, and radiation effects (model 1), was significantly higher than that of the low group (HR, 1.55; 95% confidence interval (CI), 1.23−1.95). In model 2 (model 1 plus fasting plasma glucose) and model 3 (model 1 plus HbA1c), the multivariate HRs for cancer mortality were 1.46 (95% CI, 1.15−1.85) and 1.48 (95% CI, 1.17−1.87), respectively.
The HR for cancer death at high FIRI levels (per 1 μU/mL) was 1.04 (95% CI, 1.02−1.05) in all participants after adjusting for fasting plasma glucose level and other confounders. In the subgroup analysis, the HRs were 1.03 (95% CI, 0.98−1.09), 1.05 (95% CI, 1.02−1.08), and 1.04 (95% CI, 1.02−1.06) in the normal, prediabetes, and diabetes group, respectively.
Conclusions: Hyperinsulinemia was associated with a high risk of cancer mortality and may be an important link between cancer mortality and diabetes or prediabetes.

1. Introduction

Individuals with diabetes have high risk of cancer [1–9]. In 2010, the American Diabetes Association and the American Cancer Society showed that patients with diabetes also have high risk of liver, pancreatic, endometrial, colorectal, breast, and bladder cancer [10,11]. In 2013, the Japan Diabetes Society established the Japan Diabetes Society/Japanese Cancer Association (JDS/JCA) Joint Committee on Diabetes and Cancer. According to their report, diabetes is associated with an increased risk of cancer, especially colorectal, liver, and pancreatic cancer [12]. In addition, those with prediabetes are associated with a high risk of cancer [13–15].

Hyperinsulinemia, which is induced by insulin resistance, is common in individuals with type 2 diabetes, prediabetes, and obesity, and may also have a role in tumor initiation and progression in insulin-resistant patients. There are few studies regarding the relationship between hyperinsulinemia and cancer mortality in Caucasians [16,17]; however, to our knowledge, there are none in Asians. A comparison of cancer risk among racial groups showed that Asian men and women with diabetes had a higher risk for cancer than their non-Asians counterparts [9] despite the former having comparatively lower obesity rates. Therefore, we clarified the association between hyperinsulinemia and cancer mortality in Japanese individuals.

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2. Subjects and methods

2.1. Data sources

We assessed Japanese individuals living in Hiroshima City having a fixed population of atomic bomb survivors, who were born before May 1946 and received health examinations according to Japanese medical laws. We conducted follow-ups with the cooperation of the Department of Epidemiology, Research Institute for Radiation and Medicine, Hiroshima University [18].

2.2. Study subjects

A total of 12,464 men and women, who did not receive medication for diabetes, underwent a health examination and a 75-g oral glucose tolerance test (OGTT) between 1994 and 2012. We excluded 114 men and women who were within 1 km from the hypocenter to avoid the effects of radiation on cancer mortality [19]. We also excluded 48 patients with severe inflammatory disease or malignancy at baseline, 17 who died within 1 year after registration in the study, and 47 without measurements of fasting immunoreactive insulin (FIRI) levels. Therefore, we assessed 12,238 individuals (5586 men with a mean age of 66.7 years, standard deviation [SD], 6.6 years; and 6652 women with a mean age of 68.1 years, SD, 7.0 years).

2.3. Definition of outcomes

Mortality among the participants was prospectively assessed until August 2013. Causes of death were based on death certificates and medical records. Individual diagnoses were classified using the International Classification of Death (9th edition). Solid cancer deaths were defined as code 140–199. We distinguished hematology neoplasm (ICD, 200–208) from the definition of cancer death to eliminate the influence of radiation effects [19].

2.4. Baseline examination

All participants underwent an OGTT at 8:30 a.m. after an overnight fast ($\geq$12 h), and their plasma glucose levels were measured by the glucose oxidase method. Glucose tolerance status was defined according to the 2010 diagnostic criteria of the Japan Diabetes Society [20]. The participants were divided into diabetic (DM), borderline (prediabetes), and normal glucose tolerance groups (NGT).

The participants' glycated hemoglobin (HbA1c) levels were measured by high-performance liquid chromatography or immunoassay method, which were calibrated using whole-blood standard from the Japanese Diabetes Society. The data were converted using the National Glycohemoglobin Standardization Program converter [20].

The participants' immunoreactive insulin (IRI) levels were measured by an enzyme immunoassay method. Total IRI levels were calculated by adding the fasting, 0.5-h, 1-h, 2-h, and 3-h IRI levels to the OGTT.

Fasting serum samples were used to perform liver function, renal function, and lipid tests. Anthropometric measurements (height and body weight) were performed while the participants were wearing thin clothes, and blood pressure was measured from the right arm while the participants were sitting. Electrocardiography and chest radiography were also performed.

Nurses interviewed the participants and obtained their medical history, family history, medications, and smoking habits. In addition, alcohol intake was evaluated by a dietitian, and the participants were classified as non-drinkers, mild drinkers (ethanol intake of 0.1–30 g/day), and drinkers (ethanol intake of >30 g/day).

The participants were also divided into 3 groups according to radiation exposure status: those that were within 2 km from the hypocenter, those over 2 km from the hypocenter, and those with early entrance.

2.5. Ethical considerations

This study was approved by the Central Institutional Review Board of the Hiroshima Atomic Bomb Casualty Council Health Management and Promotion Center. Informed consent was obtained from the participants, and their data were anonymized to the researchers.

2.6. Statistical analyses

Differences in the baseline characteristics among participants with NGT, prediabetes, or DM were evaluated using the Kruskal-Wallis and chi-square test for continuous and categorical variables, respectively. We conducted Cox regression to clarify the association between DM or prediabetes status and cancer mortality with multivariate adjustments for possible confounders such as age, sex, body mass index, smoking status, alcohol intake, and radiation effects (model 1).

The participants were divided into 3 groups (low, middle, and high) according to the tertiles of their FIRI level. Differences in the baseline characteristics among the 3 groups of participants according to the tertiles of FIRI levels were evaluated using the Kruskal-Wallis and chi-square test for continuous and categorical variables, respectively. The cancer mortality rate was calculated per 1000 person-years.

We assessed cancer mortality risk by FIRI level by comparing the FIRI groups to the low FIRI level group with multivariate adjustment by Cox proportional hazards model (model 1). Fasting plasma glucose or HbA1c level was also added to the factors in model 1 (model 2 or model 3).

In addition, the association of FIRI levels with cancer mortality was assessed using the FIRI level as a continuous value with multivariate adjustment for model 2 or model 3 in all participants. The association between FIRI level and cancer mortality was assessed by parametric and nonparametric models such as the spline regression. The subgroup analysis of cancer mortality risk using continuous FIRI level was performed for each glucose tolerance status. Proportional hazards assumptions were assessed using log-log curves and Shoenfeld residuals.

All analyses were performed using JMP software (SAS Institute, Cary, NC) and R-3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided and 95% confidence intervals were calculated using Wald method.

3. Results

3.1. Clinical characteristics at baseline

There were 5774, 4857, and 1607 participants with NGT, prediabetes, and DM, respectively, at registration. The clinical characteristics of these 3 groups are shown in Table 1.

3.2. Outcome

The median follow-up period was 10.0 (inter quartile range, 6.1–14.0) years, and 1008 men and 794 women died during follow-up. According to their death certificates, 355 men and 232 women died of solid cancer (ICD, 140–199), 29 men and 21 women died of leukemia (ICD, 200–208), 143 men and 84 women died of infection

Table 1
Baseline characteristics according to OGTT results.

	NGT	Prediabetes	DM	p-value
	(n = 5774)	(n = 4857)	(n = 1607)	
Age (years)	67.5 (6.8)	67.7 (6.7)	66.6 (7.2)	<0.001
Male sex	2275 (39.4)	2490 (51.3)	821 (51.1)	<0.001
BMI (kg/m^2)	22.6 (3.0)	23.6 (3.2)	24.7 (3.5)	<0.001
FPG (mmol/L)	5.2 (0.4)	5.7 (0.5)	7.0(1.5)	<0.001
1-h PG (mmol/L)	7.2 (1.6)	10.7 (2.0)	14.4 (2.9)	<0.001
2-h PG (mmol/L)	5.9 (1.1)	8.1 (1.6)	13.7 (3.7)	<0.001
FIRI (μU/mL)	5.3 (2.9)	6.6 (3.9)	8.9 (6.2)	<0.001
Total IRI (μU/mL)	86.7 (54.3)	122.6 (78.5)	118.9 (85.4)	<0.001
HbA1c (%)	5.5 (0.3)	5.7 (0.4)	6.5 (1.0)	<0.001
HbA1c (mmol/mol)	37 (3)	39 (4)	48 (11)	<0.001
Current smoker	707 (12.2)	795 (16.4)	335 (20.9)	<0.001
Alcohol consumption				
Non-drinker	3671 (63.6)	2687 (55.3)	922 (57.4)	<0.001
0.1−30.0 g/day	1454 (25.2)	1308 (26.9)	389 (24.2)	
≥30.1 g/day	649 (11.2)	862 (17.8)	296 (18.4)	
Radiation exposure status				
Within 2.0 Km	958 (16.6)	766 (15.8)	282(17.6)	<0.05
Over 2.0 Km	2360 (40.9)	1902 (39.2)	597 (37.2)	
Early entrance	2456 (42.5)	2189 (45.1)	728 (45.3)	
No. of events	190	269	128	
Event rate (per 1000 person-year)	3.38	5.40	6.98	
Adjusted HR; model 1	1.0	1.46 (1.21−1.76)	2.05 (1.62−2.57)	

Data are mean (SD) or n (%). p for trend: p-value for intergroup comparisons using the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables.
Adjusted HR; model 1: HRs adjusted for age, sex, body mass index, smoking status, alcohol intake, and radiation effect using a multiple Cox proportional hazard model.
OGTT: oral glucose tolerance test, NGT: normal glucose tolerance, Prediabetes: impaired fasting glycemia and/or impaired glucose tolerance, DM: diabetes mellitus, BMI: body mass index, FPG: fasting plasma glucose, PG: plasma glucose, FIRI: fasting immunoreactive insulin, Total IRI: adding fasting, 0.5-h, 1-h, 2-h, and 3-h immunoreactive insulin, HbA1c: glycated hemoglobin. HR: hazard ratio.

(ICD, 1−139, 460−466, 481−487), 91 men and 107 women died of cerebrovascular disease (ICD, 450−438), 68 men and 47 women died of ischemic heart disease (ICD, 410−414), 26 men and 16 women died of liver disease (ICD, 570−573), and 24 men and 15 women died of kidney disease (ICD, 580−589).

Among the 355 men who died of solid cancer, 95 died of lung cancer, 49 of liver cancer, 47 of stomach cancer, 36 of pancreatic cancer, 28 of colon cancer, 14 of esophageal cancer, 13 of kidney cancer, 12 of gall bladder cancer, 12 of prostate cancer, 10 of bladder cancer, and 39 of other cancers. Among the 232 women who died of cancer, 40 died of lung cancer, 40 of stomach cancer, 36 of pancreatic cancer, 29 of liver cancer, 19 of colon cancer, 12 of gall bladder cancer, 11 of breast cancer, 7 of uterine cancer, 6 of esophageal cancer, 5 of bladder cancer, and 27 of other cancers.

3.3. Cancer mortality according to the OGTT results

The event rates for cancer death in the participants with NGT, prediabetes, and DM were 3.38, 5.40, and 6.98 per 1000 person-year, respectively. The multivariate HRs (adjusted for age, sex, body mass index, smoking status, alcohol intake, and radiation effects) for cancer mortality were 1.46 (95% CI, 121−1.76) and 2.05 (95% CI, 1.62−2.57) in prediabetes and DM subjects, respectively, compared with the NGT subjects (Table 1).

3.4. Baseline characteristics according to the tertiles of FIRI level

Table 2 shows the characteristics of the participants in the low, medium, and high FIRI level groups. The participants in the middle and high groups had higher FPG, 1-h PG, 2-h PG, 3-h PG and HbA1c than those in the low group. The highest proportion of those with prediabetes or diabetes was found in the high group.

Table 2
Baseline characteristics according to the tertiles of FIRI.

FIRI group	Low	Middle	High	p-value
N	4413	4595	3230	
Age (years)	68.0 (6.6)	67.2 (6.9)	67.1 (6.9)	<0.001
BMI (kg/m^2)	21.6 (2.7)	23.3 (2.8)	25.5 (3.2)	<0.001
Male sex	2123 (48.1)	1983 (43.2)	1480 (45.8)	<0.001
FPG (mmol/L)	5.4 (0.7)	5.6 (0.8)	6.0 (1.1)	<0.001
1-h PG (mmol/L)	8.8 (2.9)	9.4(3.0)	10.8 (3.3)	<0.001
2-h PG (mmol/L)	7.0 (2.6)	7.7 (2.8)	9.1 (3.6)	<0.001
3-h PG (mmol/L)	5.4 (2.1)	5.8 (2.2)	6.7 (3.0)	<0.001
Glucose tolerance status				
NGT	2615 (59.3)	2210 (48.1)	949 (29.4)	<0.001
Prediabetes	1507 (34.2)	1869 (40.7)	1481 (45.9)	
DM	291 (6.6)	516 (11.2)	800 (24.8)	
FIRI (μU/mL)	3.1(0.9)	5.8 (0.8)	11.3 (4.7)	<0.001
Total IRI (μU/mL)	66.7 (32.3)	97.8 (47.3)	168.4 (92.9)	<0.001
HbA1c (%)	5.6 (0.5)	5.7 (0.5)	5.9 (0.7)	<0.001
HbA1c (mmol/mol)	38 (5)	39 (6)	41 (8)	<0.001
Current smoker	753 (17.1)	613 (13.3)	471 (14.6)	<0.001
Alcohol consumption				
Non-drinker	2436 (55.2)	2806 (61.1)	2038 (63.1)	<0.001
0.1−30.0 g/day	762 (17.3)	616 (13.4)	429 (13.3)	
Over 30.1 g/day	1215 (27.5)	1173 (25.5)	763 (23.6)	
Radiation exposure status				
Within 2.0 Km	713 (16.2)	710 (15.5)	583 (18.1)	<0.05
Over 2.0 Km	1729 (39.2)	1841 (40.1)	1289 (40.0)	
Early entrance	1971 (44.7)	2044 (44.5)	1358 (42.0)	

Data are mean (SD) or n (%). p-value for intergroup comparisons using the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables. BMI: body mass index, FPG: fasting plasma glucose, PG: plasma glucose, NGT: normal glucose tolerance, Prediabetes: impaired fasting glycemia and/or impaired glucose tolerance, DM: diabetes mellitus, FIRI: fasting immunoreactive insulin, Total IRI: adding fasting, 0.5-h, 1-h, 2-h, and 3-h immunoreactive insulin.

3.5. Cancer mortality according to the tertiles of FIRI level

The event rates for solid cancer death in the low, middle, and high FIRI level groups were 4.4, 4.4, and 5.5 per 1000 person-year, respectively (Table 3).

3.6. Risk of cancer mortality according to the tertiles of FIRI level

The HRs for cancer mortality in the participants in the middle and high FIRI level groups are shown in Table 3. The HR in the high IRI group, which was adjusted for age, sex, body mass index, smoking status, alcohol intake, and radiation effects, was significantly higher than that in the low group (model 1: HR, 1.55; 95% CI, 1.14−1.55) using multiple Cox proportional hazard model.

In the second multivariable model (model 2: model 1 plus fasting plasma glucose), the multivariate HR in the high group was also significantly higher than that in the low group (HR, 1.46; 95% CI, 1.15−1.85).

In the third multivariable model (model 3: model 1 plus HbA1c), the multivariate HR in the high group was also significantly higher than that in the low group (HR, 1.48; 95% CI, 1.17−1.87).

3.7. Risk of cancer mortality according to FIRI level and glucose tolerance status

The association of FIRI level, as a continuous value, with cancer mortality was evaluated using a spline regression; however, its association was similar to that of a linear relationship. The HR for cancer death at high FIRI levels (per 1 μU/mL) in model 2 and model 3 were 1.04 (95% CI, 1.02−1.05) and 1.04 (95% CI, 1.02−1.05), respectively, in all participants. The HRs for cancer death at high FIRI levels in model 2 were 1.03 (95% CI, 0.98−1.09), 1.05 (95% CI, 1.02−1.08), and 1.04 (95% CI, 1.02−1.06) in normal, prediabetes, and DM groups, respectively. The HRs for cancer death at high FIRI levels in model 3 were 1.02 (95% CI, 0.96−1.07), 1.05 (95% CI, 1.02−1.08), and 1.03 (95% CI, 1.02−1.05) in normal, prediabetes, and DM groups, respectively (Table 4).

4. Discussion

We clarified the relationship between cancer mortality and hyperinsulinemia in Japanese individuals and showed that hyperinsulinemia was associated with an increased risk of cancer death.

There are several studies regarding the relationship between hyperinsulinemia and cancer risk. In a mouse model of transplanted breast cancer, endogenous hyperinsulinemia was associated with insulin resistance as well as promoted cancer proliferation and metastasis independent of hyperglycemia or obesity [21]. To our knowledge, ours is the first prospective cohort study to clarify the association between hyperinsulinemia and cancer mortality in Asians.

Although the mechanism linking diabetes or prediabetes and cancer risk are unclear, hyperglycemia and chronic inflammation as well as hyperinsulinemia may play a role. A possible mechanism for oncogenesis associated with insulin resistance and hyperinsulinemia is that compensatory hyperinsulinemia occurs in order to decrease the production of insulin-like growth factor binding proteins 1 and 2. As a result, insulin-like growth factor 1 (IGF-1) activity increases, and, since both insulin and IGF-1 are able to induce cell proliferation and inhibit cell apoptosis through their receptors, it may lead to onset or progression of cancer [22,23].

In this study, after adjusting for common cancer risks, the HR for cancer mortality of participants with high FIRI levels was significantly higher (model 1: HR, 1.55) than those with low FIRI levels. However, the group with high FIRI levels also had a large proportion of those with DM and prediabetes. In this study, the HRs for cancer mortality were 2.05-fold and 1.46-fold higher in participants with DM and prediabetes, respectively. Therefore, we added fasting plasma glucose or HbA1c as a factor in the analysis (model 2 or model 3). We found that the participants with hyperinsulinemia had high risk for cancer death independent of hyperglycemia.

Moreover, we assessed FIRI levels, as a continuous value, as a risk for cancer mortality. FIRI levels had a linear relationship with cancer mortality using spline regression. Therefore, we conducted a study using multiple Cox proportional hazards model. We added fasting plasma glucose or HbA1c level as a factor for adjustment. The HR for cancer death for those with high FIRI levels was significantly high compared with those with lower FIRI levels. We conducted a subgroup analysis to assess the association of FIRI levels with cancer mortality risk based on glucose tolerance status. The HRs for cancer death at high FIRI levels were significantly high in prediabetes and DM participants. Therefore, hyperinsulinemia may be associated with an increased risk of cancer mortality, particularly in those with diabetes and pre-diabetes. It may be important to control not only hyperglycemia but also hyperinsulinemia in order to reduce cancer mortality rate. Future intervention studies based on lifestyle changes or those using therapeutic agents to suppress hyperinsulinemia are required.

This study had several strengths such as the inclusion of a large cohort. In addition, the definitions of DM, prediabetes, and NGT were based on the results of an OGTT. Furthermore, all tests,

Table 3
Cancer mortality according to the tertiles of FIRI.

FIRI group	Low	Middle	High
N	4413	4595	3230
No. of cancer death	178	217	192
Event rate (per 1000 person-year)	4.4	4.4	5.5
Adjusted HR; model 1	1.0	1.14 (0.93−1.40)	1.55 (1.23−1.95)
Adjusted HR; model 2	1.0	1.12 (0.91−1.37)	1.46 (1.15−1.85)
Adjusted HR: model 3	1.0	1.13 (0.92−1.39)	1.48 (1.17−1.87)

Adjusted HR; model 1: HRs adjusted for age, sex, body mass index, smoking status, alcohol intake, and radiation effect using a multiple Cox proportional hazard model.
Adjusted HR; model 2: model 1 plus fasting plasma glucose.
Adjusted HR; model 3: model 1 plus HbA1c.
FIRI: fasting immunoreactive insulin, HR: hazard ratio.

Table 4
Risk for cancer mortality of FIRI value (per 1 μU/mL) in all participants and in each glucose tolerance status.

	Adjusted HR	95%CI	P value
Model 2			
All participants	1.04	1.02−1.05	<0.001
NGT	1.03	0.98−1.09	0.225
Prediabetes	1.05	1.02−1.08	<0.001
DM	1.04	1.02−1.06	<0.001
Model 3			
All participants	1.04	1.02−1.05	<0.001
NGT	1.02	0.96−1.07	0.584
Prediabetes	1.05	1.02−1.08	<0.001
DM	1.03	1.02−1.05	<0.001

Model 2: HRs adjusted for age, sex, body mass index, smoking status, alcohol intake, radiation effect, and fasting plasma glucose using a multiple Cox proportional hazard model.
Model 3: HRs adjusted for age, sex, body mass index, smoking status, alcohol intake, radiation effect, and HbA1c using a multiple Cox proportional hazard model.
FIRI: fasting immunoreactive insulin, HR: hazard ratio, NGT: normal glucose tolerance, Prediabetes: impaired fasting glycemia and/or impaired glucose tolerance, DM: diabetes mellitus.

including IRI, were performed using the same methods, and the participants were interviewed using the same protocol, which allowed us to address confounding factors such as smoking status and alcohol intake. Moreover, the complete prognoses of most participants were available.

The study also had several limitations. First, the categorization of hyperinsulinemia was based on a single measurement of FIRI level. Second, although most participants had previously undergone annual cancer-screening examinations, such as chest radiography, upper gastrointestinal examination, stool tests, mammography, and cervical cytology, it is possible that some had latent cancer at registration. To mitigate this issue, we excluded participants who died within 1 year after registration. Third, in the multivariable analysis, other potential risk factors for cancer (e.g., occupation, food intake, physical activities, etc.) were not assessed. Fourth, most participants were survivors of an atomic bomb, and radiation may have influenced the occurrence of cancer. According to the Japan Ministry of Health, Labor and Welfare [24], cancer is the most common cause of Japanese deaths. The next most common cause is infection, and the third is cerebrovascular disorders. In our study, we found similar results. Nationally, the first, second, and third most common causes of organ-specific cancer deaths in Japanese men are lung, gastric, and colon cancer, respectively. In Japanese women, the first, second, and third most common causes are colon, lung, and pancreatic cancer, respectively. In our study, the first, second, and third most common causes of organ-specific cancer were lung, liver, and gastric cancer, respectively, and in women, they were lung, gastric, and pancreatic cancer, respectively. Compared with the national results, the mortality rate of colon cancer in our subjects was low. This may be due to differences in age distribution between our subjects and those nationwide. Therefore, our subjects were similar to those of the general Japanese population despite having being exposed to radiation. Furthermore, we added radiation exposure status to the analysis as an adjustment factor. Fifth, the outcome of this study was cancer mortality. Therefore, it was difficult to assess whether the increased cancer mortality of those with hyperinsulinemia was attributable to cancer onset or development. To clarify the pathophysiological relationship between hyperinsulinemia and cancer mortality, further studies are required.

In conclusion, hyperinsulinemia was associated with a high risk of cancer mortality and may be an important link between cancer mortality and DM or prediabetes. Although hyperglycemia and hyperinsulinemia have strong causal relationships, this study showed that FIRI levels may be associated with cancer mortality independent of fasting plasma glucose or HbA1c levels.

CRediT authorship contribution statement

Sakurako Kira: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Chikako Ito:** Data curation, Supervision. **Rumi Fujikawa:** Writing - review & editing. **Munechika Misumi:** Formal analysis.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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