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Association between hyperinsulinemia and increased risk of cancer death in nonobese and obese people: A population-based observational study

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Cancer Epidemiology

Obesity, metabolic syndrome and type 2 diabetes are associated with cancer-related mortality. We assessed whether hyperinsulinemia is a risk factor for cancer death in nonobese people without diabetes. We conducted a prospective cohort study using data from the National Health and Nutrition Examination Survey 1999–2010 and followed up the participants until December 31, 2011. For the primary analysis of cancer mortality, we used Cox proportional hazard models to estimate hazard ratios (HRs) in the participants with hyperinsulinemia and those without. Hyperinsulinemia was defined as a fasting insulin level of ≥10 μU/mL. To identify causes of deaths, the *International Classification of Diseases, Tenth Revision* codes were used. This study included 9,778 participants aged 20 years or older without diabetes or a history of cancer: 6,718 nonobese participants (2,057 with hyperinsulinemia [30.6%]) and 3,060 obese participants (2,303 with hyperinsulinemia [75.3%]). A total of 99.9% completed follow-up. Among all study participants, cancer mortality was significantly higher in those with hyperinsulinemia than in those without hyperinsulinemia (adjusted HR 2.04, 95% CI 1.24–3.34, $p = 0.005$). Similarly, among nonobese participants, multivariable analysis showed that cancer mortality was significantly higher in those with hyperinsulinemia than in those without (adjusted HR 1.89, 95% CI 1.07–3.35, $p = 0.02$). Considering that nonobese people with hyperinsulinemia were at higher risk of cancer mortality than those without hyperinsulinemia, improvement of hyperinsulinemia may be an important approach for preventing cancer regardless of the presence or absence of obesity.

The global prevalence of obesity has increased markedly over the past three decades, and its incidence continues to accelerate.[1,2] Overweight and obesity were estimated to cause 3.4 million deaths in 2010.[3] Excess weight is an important risk factor not only for cardiovascular diseases but also for cancer.[4] Recent studies have suggested that diabetes and metabolic syndrome are associated with an increased risk of cancer and cancer-related death.[5,6] Although the pathophysiological mechanisms remain unclear, many obesity-related factors such as hyperinsulinemia and inflammation may increase cancer risk via their influences on neoplastic processes.[7,8] However, hyperinsulinemia also occurs in nonobese

Key words: hyperinsulinemia, cancer, cancer mortality, obesity, nonobesity

Abbreviations: BMI: body-mass index; CI: confidence interval; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; HR: hazard ratio; IGF-1: insulin-like growth factor 1; ; MECs: mobile examination centers; NCHS: National Center for Health Statistics; NHANES: National Health and Nutrition Examination Survey; SD: standard deviation; WHO: World Health Organization

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What's new?

Obesity, metabolic syndrome, and type 2 diabetes are associated with cancer-related mortality, with hyperinsulinemia possibly playing a role. However, hyperinsulinemia also occurs in nonobese people. So far, no study has investigated whether hyperinsulinemia in nonobese people without diabetes is associated with increased risks of cancer-related death. This prospective cohort study shows that among nonobese people, hyperinsulinemia was associated with a significantly higher risk of cancer mortality. Furthermore, hyperinsulinemia was associated with an increased risk of cancer death in people with normal fasting plasma glucose levels. Improvement of hyperinsulinemia may thus be an important approach for preventing cancer regardless of obesity.

people. In fact, apart from obesity, race/ethnicity, sex, physical activity, and genetic factors are important contributors to insulin resistance and hyperinsulinemia.[9,10] Hyperinsulinemia may promote cancer independent of obesity as insulin can exert its oncogenic potential via abnormal stimulation of multiple cellular signaling cascades;[11] however, no study has investigated whether hyperinsulinemia in nonobese people without diabetes is similarly associated with increased risks of cancer and cancer-related death. Therefore, using nationally representative data, we assessed whether hyperinsulinemia was a risk factor for cancer death in nonobese people without diabetes. In addition, a previous study suggested that elevated fasting glucose levels are an independent risk factor of cancer death.[12] We assessed whether higher glucose levels were associated with an increased risk of cancer death in people without diabetes.

Material and Methods

Data source and study population

This was a prospective cohort study using data from the continuous National Health and Nutrition Examination Survey (NHANES) 1999–2010.[13] The NHANES is a cross-sectional survey with linked follow-up data. The cross-sectional survey is conducted every 2 years by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention in the US. It uses a stratified, multistage probability sampling design, which enables representation of the US civilian noninstitutionalized population.[13] In this study, data were collected at people's homes and at mobile examination centers (MECs). Blood specimens were collected during the MEC examinations. Written informed consent was obtained from all participants. The NCHS Research Ethics Review Board approved the NHANES protocols.[14]

Among the population participating in the NHANES during 1999–2010, the unweighted response rate of household interviews was 80.6% and that of MEC examinations was 77.1%.[15] We focused on fasting insulin levels in participants aged 20 years or older without diabetes or a history of cancer. Diabetes was defined as meeting one of the following four criteria: a previous diagnosis of diabetes, intake of antidiabetic medication or insulin, a fasting glucose level of $\geq$126 mg/dl or a glycated hemoglobin (HbA1c) level of $\geq$6.5%.[16] History of cancer was defined as a previous diagnosis of cancer/malignancy. Among a total of 10,033 participants aged 20 years or older without diabetes or a history of cancer, we excluded those with missing information on body-mass index (BMI, calculated as weight [kg] divided by height [m] squared), race/ethnicity, educational attainment, smoking status, hypertension, dyslipidemia, history of cardiovascular disease or fasting plasma glucose (FPG) level. This produced a final sample of 9,778. We prospectively followed up these study participants from the date of survey participation for interviews until December 31, 2011.

Definition of hyperinsulinemia and cancer mortality

Information on fasting insulin levels was extracted from the MEC measurements in the NHANES 1999–2010. Fasting insulin levels were tested after participants had fasted for at least 9 hrs. Serum insulin was analyzed using the Pharmacia RIA assay in the NHANES 1999–2002, the Tosoh immunoenzymometric assay in the NHANES 2003–2004, the Mercodia ELISA assay in the NHANES 2005–2009 and the Roche chemiluminescent immunoassay in the NHANES 2009–2010. Median fasting insulin levels were 9.8, 9.3, 7.3, 8.4, 9.2 and 10.6 μU/mL in the NHANES 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008 and 2009–2010, respectively, and 9.2 μU/mL in all study participants. Based on these data, hyperinsulinemia was defined as a fasting insulin level of $\geq$10 μU/mL. The conversion factor for insulin is 1 μU/mL = 6.00 pmol/L. This unit conversion is based on the World Health Organization (WHO) standard adopted in 1987 based on human insulin with a potency of 26,000 U/g.[17,18]

The primary endpoint was cancer mortality. We used the mortality follow-up data that were provided in the Public-use Linked Mortality Files.[19] To identify causes of deaths occurring in participants in or after 1999, the NHANES used the *International Classification of Diseases, Tenth Revision* codes.[20] The specific code was C00–C97 for causes of death from malignant neoplasms.

Other measurements

We extracted data on potential confounders, including age, sex, race and ethnicity, education attainment, smoking status, BMI, hypertension, dyslipidemia, history of cardiovascular disease and FPG level measured upon MEC examination. We categorized age into four groups: 20–39 years, 40–59 years, 60–79 years and $\geq$80 years. Race and ethnicity were classified as non-Hispanic white, non-Hispanic black, Mexican American or "Others" including other Hispanics, Asian and multiracial participants. We classified educational attainment as beyond high school, high school graduation or general

Table 1. Characteristics of study participants with and without hyperinsulinemia[1]

Characteristics	All			Nonobese			Obese		
Hyperinsulinemia	(−)	(+)	*p* value	(−)	(+)	*p* value	(−)	(+)	*p* value
Unweighted participants	5,418	4,360		4,661	2,057		757	2,303	
Age, y									
20–39	45.4%	44.3%	0.46	46.3%	45.5%	0.68	39.0%	43.3%	0.06
40–59	38.6%	38.9%	0.88	38.1%	36.4%	0.41	42.6%	41.0%	0.50
60–79	13.1%	15.0%	0.01	12.6%	15.2%	0.008	16.5%	14.8%	0.33
≥ 80	2.9%	1.8%	<0.001	3.0%	2.9%	0.64	1.9%	0.9%	0.005
Female sex	54.2%	47.4%	<0.001	53.3%	42.8%	<0.001	60.6%	51.5%	0.001
Race/ethnicity									
Non-Hispanic white	73.9%	65.8%	<0.001	74.7%	64.8%	<0.001	67.8%	66.7%	0.64
Non-Hispanic black	9.8%	12.3%	<0.001	8.7%	9.5%	0.29	17.2%	14.7%	0.11
Mexican American	6.5%	10.6%	<0.001	6.5%	11.7%	<0.001	6.8%	9.7%	<0.001
Others[2]	9.8%	11.3%	0.06	10.1%	14.0%	<0.001	8.2%	8.9%	0.66
Education attainment									
< High school	16.4%	20.1%	<0.001	16.0%	20.1%	<0.001	18.7%	20.2%	0.47
High school or GED	23.5%	26.5%	0.005	23.5%	25.8%	0.05	23.8%	27.1%	0.16
> High school	60.1%	53.4%	<0.001	60.5%	54.1%	<0.001	57.5%	52.7%	0.08
Smoking status									
Never	52.6%	53.4%	0.49	52.0%	52.4%	0.76	56.8%	54.2%	0.29
Former	21.6%	25.8%	<0.001	21.4%	25.3%	0.01	22.5%	26.4%	0.07
Current	25.8%	20.8%	<0.001	26.6%	22.3%	0.004	20.7%	19.4%	0.53
Body mass index (kg/m^2)[3]	25.3 (3.6)	31.5 (5.7)	<0.001	24.1 (2.5)	26.4 (2.3)	<0.001	33.6 (2.9)	36.0 (4.9)	<0.001
< 18.5	3.0%	0.3%	<0.001	3.4%	0.6%	<0.001	–	–	
18.5–24.9	49.7%	11.7%	<0.001	57.0%	25.0%	<0.001	–	–	
25.0–29.9	34.5%	34.8%	0.85	39.6%	74.4%	<0.001	–	–	
30.0–34.9	9.6%	29.0%	<0.001	–	–		74.6%	54.4%	<0.001
≥ 35.0	3.2%	24.2%	<0.001	–	–		25.4%	45.6%	<0.001
Waist circumference (cm)	89.1 (9.7)	104.8 (12.8)	<0.001	86.6 (7.9)	94.3 (8.2)	<0.001	107.1 (7.9)	114.0 (10.7)	<0.001
Hypertension	18.1%	31.6%	<0.001	16.5%	24.8%	<0.001	28.9%	37.5%	<0.001
Dyslipidemia	44.4%	66.0%	<0.001	42.8%	63.3%	<0.001	55.2%	68.3%	<0.001
Cardiovascular disease	4.1%	6.6%	<0.001	3.9%	6.9%	<0.001	5.2%	6.4%	0.23
Fasting plasma glucose (mg/dL)	93.8 (7.2)	99.9 (8.4)	<0.001	93.5 (7.1)	99.1 (8.5)	<0.001	96.1 (7.5)	100.5 (8.3)	<0.001

[1]Data are represented as number of participants, percent, or mean (SD). An appropriate weight was used for each analysis, except for the number of participants. GED = General Educational Development.
[2]The category includes other Hispanics and other races, including multiracial participants.
[3]Body-mass index was calculated as the weight in kilograms divided by the square of height in meters.

education development certificate, or less than high school. Smoking status was classified as current, former, or never smoker. Obesity was defined as a BMI of ≥30 kg/m^2 and nonobesity was defined as a BMI of <30 kg/m^2. In all study participants, BMI was classified as <18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9 or ≥35.0 kg/m^2. BMI in obese participants was classified as 30.0–34.9 or ≥35.0 kg/m^2 and that in nonobese participants was classified as <18.5, 18.5–24.9 or 25.0–29.9 kg/m^2. Hypertension was defined as either a previous diagnosis of hypertension or intake of anti-hypertensive medication. Dyslipidemia was defined as a previous diagnosis of hypercholesterolemia, intake of lipid-lowering medication, low-density lipoprotein cholesterol ≥140 mg/dl, high-density lipoprotein cholesterol <40 mg/dl or triglycerides ≥200 mg/dl. Low-density lipoprotein cholesterol was calculated using the Friedewald equation (total cholesterol − high-density lipoprotein cholesterol − triglycerides/5) for participants examined in the morning in the fasting state who had triglyceride levels ≤400 mg/dl (triglycerides were converted to millimoles per liter by multiplying by 0.0113). History of cardiovascular

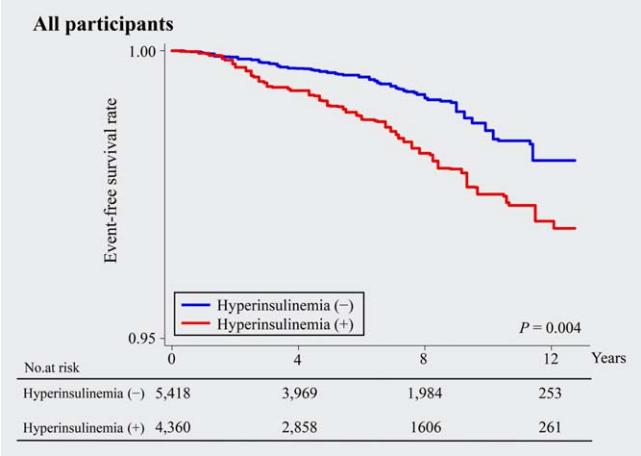

Figure 1. Rates of freedom from cancer death in participants with and without hyperinsulinemia.

disease was defined as a previous diagnosis of coronary heart disease, myocardial infarction, angina pectoris, or stroke. FPG levels were tested in participants who had fasted for at least 9 hrs.

Statistical analysis

Demographic data are presented as numbers with proportions (%) or means with standard deviations (SD). Study participants with hyperinsulinemia were compared with those without hyperinsulinemia using a *t test* for continuous variables or the χ^2 test for categorical variables. For the primary analyses of cancer mortality outcome, we used Cox proportional hazard models to analyze the unadjusted and adjusted hazard ratios (HRs) in participants with hyperinsulinemia compared with those without hyperinsulinemia. Kaplan–Meier survival curves were constructed for cancer mortality outcomes in participants with and without hyperinsulinemia. In the first multivariable model (model 1), we included age, sex, race/ethnicity, education attainment, smoking status and BMI for adjustment. In the second multivariable model (model 2), hypertension, dyslipidemia, history of cardiovascular disease and FPG (continuous) were added to the factors in model 1 for adjustment. Because of the possibility of multicollinearity between FPG and hyperinsulinemia, we conducted additional analyses in the model 2 excluding FPG. The analyses were performed for nonobese and obese participants. To explore the effect modification on hyperinsulinemia and cancer mortality by obesity status, we tested for interactions between hyperinsulinemia and obesity in the multivariable model 2. Among nonobese participants, the analyses were also performed in participants with normal weight (BMI: 18.5–25.0 kg/m^2) and with overweight (BMI: 25.0–29.9 kg/m^2). Participants with a BMI of $<$18.5 kg/m^2 may have a preexisting illness and represent some reverse causation; thus, we conducted sensitivity analyses excluding these participants. In addition, the effects of central adiposity may not have been fully adjusted even in the multivariable model 2 that includes the detailed classification of BMI; thus, we conducted further analyses with adjustment for waist circumference in addition to the potential confounders of models 1 and 2. Furthermore, we conducted similar analyses with all study participants divided into two groups according to a cut-off FPG level of 100 mg/dl, which approximated the overall mean value in this study. To exclude the potential effect of the complication of undiagnosed cancer, we conducted sensitivity analyses limited to the cancer mortality outcome with a follow-up period of $\geq$1 year. Although the NHANES measured physical activity, this variable was not included in the main analyses owing to inconsistent measurements, which changed between the 20052006 and 2007–2008 periods. Therefore, as another sensitivity analysis limited to the data from NHANES 1999–2006, physical activity was added as an adjustment to model 2. Physical activity was divided into two groups according to a cutoff value of 150 min per week of walking and/or bicycling.[21]

All statistical analyses were conducted using Stata software (version 14.1, Stata Corp, College Station, Texas, USA), accounting for the complex survey design. We used an appropriate weight for each analysis, based on the variables selected. These weights accounted for unequal probabilities of selection and nonresponses to make unbiased national estimates. *P* values of $<$0.05 were considered statistically significant. Given the lack of statistical power inherent in interaction tests, we used a *p* values cut point of $<$0.2 for such tests.[22]

Results

The characteristics of the participants with and without hyperinsulinemia are presented in Table 1. The study included 6,718 nonobese participants (2,057 with hyperinsulinemia [30.6%]) and 3,060 obese participants (2,303 with hyperinsulinemia [75.3%]). Among nonobese participants, hyperinsulinemia was associated with more proportion of male sex, race/ethnicity of Mexican-American or Others, education attainment of less than high school, and former smoking, higher BMI, more prevalence of hypertension, dyslipidemia and cardiovascular disease, and higher FPG levels. Among obese participants, hyperinsulinemia was associated with more proportion of male sex, and Mexican-American, higher BMI, more prevalence of hypertension and dyslipidemia, and higher FPG levels.

Kaplan–Meier survival curves and event rates for cancer death of all study participants with and without hyperinsulinemia are shown in Figure 1 and Table 2, respectively. The mean ($\pm$SD) follow-up period in all study participants was 6.7 ($\pm$2.9) years. A total of 99.9% completed follow-up and a total of 144 cancer deaths were reported. The event rates for cancer death in participants with and without hyperinsulinemia were 2.2 and 1.1 per 1,000 person–years, respectively, and unadjusted and age- and sex-adjusted HRs (95% confidence intervals [CI]) for cancer death were significantly higher in participants with hyperinsulinemia than in those

Table 2. Risk for cancer mortality in participants with and without hyperinsulinemia[1]

Characteristics	Hyperinsulinemia (−)	Hyperinsulinemia (+)	*p value*
All participants			
No. of events/total participants	75/5,418	69/4,360	
Event rate (per 1,000 person-year)	1.1	2.2	
Unadjusted HR (95% CI)	1.00 [ref]	1.93 (1.23–3.01)	0.004
Age and sex adjusted HR (95% CI)	1.00 [ref]	1.82 (1.16–2.83)	0.009
Model 1: adjusted HR (95% CI)[2]	1.00 [ref]	2.04 (1.27–3.28)	0.004
Model 2: adjusted HR (95% CI)[3]	1.00 [ref]	2.04 (1.24–3.34)	0.005
Men			
No. of events/total participants	58/2,518	48/2,102	
Event rate (per 1,000 person-year)	1.8	2.9	
Unadjusted HR (95% CI)	1.00 [ref]	1.61 (0.99–2.60)	0.05
Age adjusted HR (95% CI)	1.00 [ref]	1.56 (0.95–2.58)	0.07
Model 1: adjusted HR (95% CI)	1.00 [ref]	2.08 (1.22–3.56)	0.008
Model 2: adjusted HR (95% CI)	1.00 [ref]	2.15 (1.26–3.70)	0.006
Women			
No. of events/total participants	17/2,900	21/2,258	
Event rate (per 1,000 person-year)	0.6	1.6	
Unadjusted HR (95% CI)	1.00 [ref]	2.55 (1.08–5.99)	0.03
Age adjusted HR (95% CI)	1.00 [ref]	2.64 (1.14–6.15)	0.02
Model 1: adjusted HR (95% CI)	1.00 [ref]	1.91 (0.79–4.68)	0.15
Model 2: adjusted HR (95% CI)	1.00 [ref]	1.78 (0.67–4.72)	0.24
Nonobese participants[4]			
No. of events/total participants	70/4,661	40/2,057	
Event rate (per 1,000 person-year)	1.2	2.6	
Unadjusted HR (95% CI)	1.00 [ref]	2.10 (1.23–3.58)	0.007
Age and sex adjusted HR (95% CI)	1.00 [ref]	1.84 (1.08–3.17)	0.02
Model 1: adjusted HR (95% CI)	1.00 [ref]	1.96 (1.12–3.45)	0.01
Model 2: adjusted HR (95% CI)	1.00 [ref]	1.89 (1.07–3.35)	0.02
Obese participants[5]			
No. of events/total participants	5/757	29/2,303	
Event rate (per 1,000 person-year)	0.8	1.9	
Unadjusted HR (95% CI)	1.00 [ref]	2.31 (0.61–8.72)	0.21
Age and Sex adjusted HR (95% CI)	1.00 [ref]	2.22 (0.60–8.29)	0.23
Model 1: adjusted HR (95% CI)	1.00 [ref]	2.38 (0.67–8.38)	0.17
Model 2: adjusted HR (95% CI)	1.00 [ref]	2.59 (0.68–9.86)	0.16

[1]Data are presented as number or HR (95% CI). An appropriate weight was used for each analysis, except for the number of events and total number. CI = confidence interval; HR = hazard ratio.
[2]Multivariable model 1 was made by adjusting for age (20–39, 40–59, 60–79, 80 y or older), sex (male or female), race and ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and others), educational attainment (more than high school, high school graduation or General Education Development certificate, or less than high school), smoking status (current, former, or never smoker), and body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, and ≥35.0 kg/m^2).
[3]Multivariable Model 2 was made by adjusting for age (20–39, 40–59, 60–79, 80 y or older), sex, race and ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and others), educational attainment (more than high school, high school graduation or General Education Development certificate, or less than high school), smoking status (current, former, or never smoker), body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, and ≥35.0 kg/m^2), hypertension, dyslipidemia, history of cardiovascular disease, and fasting plasma glucose levels (continuous).
[4]Body mass index for multivariable adjustment model 1 and 2 was divided into three groups: <18.5, 18.5–24.9, and 25.0–29.9 kg/m^2.
[5]Body mass index for multivariable adjustment model 1 and 2 was divided into two groups: 30.0–34.9 and ≥35.0 kg/m^2.

without hyperinsulinemia (unadjusted HR 1.93, 95% CI 1.23–3.01, $p = 0.004$; age- and sex-adjusted HR 1.82, 95% CI 1.16–2.83, $p = 0.009$). Using multivariable Cox proportional hazard models, cancer mortality was significantly higher in the participants with hyperinsulinemia than in those without (model 1: HR 2.04, 95% CI 1.27–3.28, $p = 0.004$; model 2: HR 2.04, 95% CI 1.24–3.34, $p = 0.005$). Similar results were observed in the model 2 when FPG was excluded (HR 2.10, 95% CI 1.29–3.44, $p = 0.003$). The analyses including waist circumference did not change the results (model 1 with waist circumference: HR 1.98, 95% CI 1.19–3.30, $p = 0.009$; model 2 with waist circumference: HR 1.97, 95% CI 1.17–3.34, $p = 0.01$). Similarly, cancer mortality in men was significantly higher in those with hyperinsulinemia than in those without hyperinsulinemia (model 1: HR 2.08, 95% CI 1.22–3.56, $p = 0.008$; model 2: HR 2.15, 95% CI 1.26–3.70, $p = 0.006$). Among female participants, cancer mortality was not significantly higher in those with hyperinsulinemia than in those without (model 1: HR 1.91, 95% CI 0.79–4.68, $p = 0.15$; model 2: HR 1.78, 95% CI 0.67–4.72, $p = 0.24$). Furthermore, to assess whether the results differed between assays, we conducted sensitivity analyses stratified by the survey years: 1999–2002 for the Pharmacia RIA assay, 2003–2004 for the Tosoh immunoenzymometric assay, 2005–2008 for the Mercodia ELISA assay and 2009–2010 for the Roche chemiluminescent immunoassay. Compared with those without hyperinsulinemia, the adjusted HRs in the multivariable model 2 in those with hyperinsulinemia varied (1999–2002: HR 1.40, 95% CI 0.75–2.58; 2003–2004: HR 1.93, 95% CI 0.60–6.21; 2005–2008: HR 6.53, 95% CI 3.04–14.02; 2009–2010: HR 2.26, 95% CI 0.39–13.09).

In nonobese participants, cancer mortality was significantly higher in those with hyperinsulinemia than in those without hyperinsulinemia (unadjusted HR 2.10, 95% CI 1.23–3.58, $p = 0.007$) (Fig. 2*a*). In obese participants, cancer mortality was higher in those with hyperinsulinemia but there was no significant association between those with and without hyperinsulinemia (unadjusted HR 2.31, 95% CI 0.61–8.72, $p = 0.21$) (Fig. 2*b*). Although there was no significant association, similar results were observed in participants with overweight and those with normal weight (overweight participants: unadjusted HR 1.83, 95% CI 0.95–3.55, $p = 0.07$; normal weight participants: unadjusted HR 1.88, 95% CI 0.60–5.90, $p = 0.27$) (Supporting Information Fig. 1). Among nonobese participants, multivariable Cox proportional hazard analysis showed that cancer mortality was significantly higher in those with hyperinsulinemia than in those without (model 1: HR 1.96, 95% CI 1.12–3.45, $p = 0.01$; model 2: HR 1.89, 95% CI 1.07–3.35, $p = 0.02$). The analysis in the model 2 excluding FPG showed similar results (HR 2.04, 95% CI 1.14–3.63, $p = 0.01$). In addition, the analysis in the multivariable model 2 showed that older age, male sex, and current smoking were also significantly associated with an increased risk of cancer death in nonobese participants. The sensitivity analyses excluding participants with a BMI of <18.5 kg/m^2

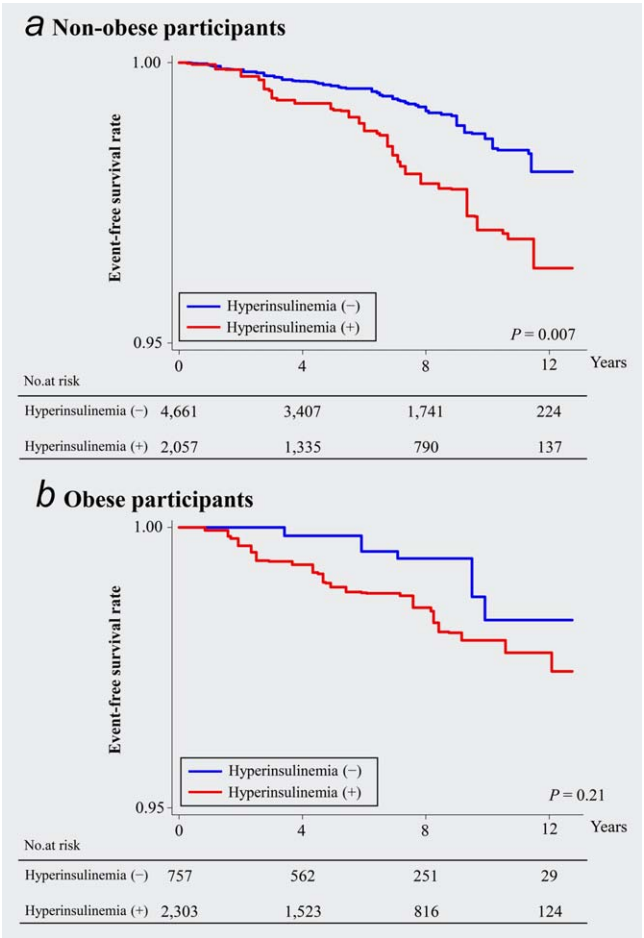

Figure 2. Rates of freedom from cancer death in nonobese and obese participants with and without hyperinsulinemia. Graphs for cancer death in nonobese (*a*) and obese (*b*) participants with and without hyperinsulinemia.

showed similar results (model 1: HR 1.87, 95% CI 1.07–3.27, $p = 0.02$; model 2: HR 1.83, 95% CI 1.04–3.22, $p = 0.03$). In addition, similar results were observed after multivariable adjustment including waist circumference (model 1 with waist circumference: HR 1.91, 95% CI 1.02–3.56, $p = 0.04$; model 2 with waist circumference: HR 1.83, 95% CI 0.97–3.45, $p = 0.06$). The HRs for cancer mortality in nonobese participants limited to the maximum follow-up periods of 1, 3 and 5 years were as follows: 1 year (model 1: HR 0.70, 95% CI 0.10–5.00, $p = 0.72$; model 2: HR 0.48, 95% CI 0.07–3.35, $p = 0.45$), 3 year (model 1: HR 2.14, 95% CI 0.80–5.70, $p = 0.12$; model 2: HR 1.92, 95% CI 0.66–5.65, $p = 0.23$) and 5 year (model 1: HR 1.71, 95% CI 0.76–3.86, $p = 0.19$; model 2: HR 1.58, 95% CI 0.66–3.77, $p = 0.29$). Although there were limited powers, cancer mortality in obese participants was not significantly higher in those with hyperinsulinemia than in those without (model 1: HR 2.38, 95% CI 0.67–8.38, $p = 0.17$; model 2: HR 2.59, 95% CI 0.68–9.86, $p = 0.16$). The results did not change in the analysis in the model 2 when FPG was excluded (HR 2.46, 95% CI 0.67–8.99, $p = 0.17$). The analysis in the multivariable model 2 showed that other

Table 3. Risk for cancer mortality in participants limited to the outcome with a follow-up period of at least 1 year[1]

Characteristics	Hyperinsulinemia (−)	Hyperinsulinemia (+)	*p value*
All participants			
No. of events/total participants	70/5,418	66/4,360	
Event rate (per 1,000 person-year)	1.1	2.2	
Unadjusted HR (95% CI)	1.00 [ref]	1.96 (1.24–3.10)	0.004
Age and sex adjusted HR (95% CI)	1.00 [ref]	1.84 (1.17–2.90)	0.009
Model 1: adjusted HR (95% CI)[2]	1.00 [ref]	2.04 (1.26–3.32)	0.004
Model 2: adjusted HR (95% CI)[3]	1.00 [ref]	2.05 (1.23–3.41)	0.006
Men			
No. of events/total participants	53/2,518	46/2,102	
Event rate (per 1,000 person-year)	1.8	2.8	
Unadjusted HR (95% CI)	1.00 [ref]	1.68 (1.03–2.76)	0.03
Age adjusted HR (95% CI)	1.00 [ref]	1.63 (0.98–2.71)	0.05
Model 1: adjusted HR (95% CI)	1.00 [ref]	2.11 (1.22–3.67)	0.008
Model 2: adjusted HR (95% CI)	1.00 [ref]	2.22 (1.27–3.86)	0.005
Women			
No. of events/total participants	17/2,900	20/2,258	
Event rate (per 1,000 person-year)	0.6	1.5	
Unadjusted HR (95% CI)	1.00 [ref]	2.40 (1.01–5.77)	0.04
Age adjusted HR (95% CI)	1.00 [ref]	2.52 (1.06–5.99)	0.03
Model 1: adjusted HR (95% CI)	1.00 [ref]	1.86 (0.75–4.66)	0.18
Model 2: adjusted HR (95% CI)	1.00 [ref]	1.68 (0.61–4.61)	0.30
Nonobese participants[4]			
No. of events/total participants	65/4,661	38/2,057	
Event rate (per 1,000 person-year)	1.1	2.5	
Unadjusted HR (95% CI)	1.00 [ref]	2.16 (1.25–3.73)	0.006
Age and sex adjusted HR (95% CI)	1.00 [ref]	1.91 (1.10–3.30)	0.02
Model 1: adjusted HR (95% CI)	1.00 [ref]	1.99 (1.12–3.52)	0.01
Model 2: adjusted HR (95% CI)	1.00 [ref]	1.95 (1.09–3.48)	0.02
Obese participants[5]			
No. of events/total participants	5/757	28/2,303	
Event rate (per 1,000 person-year)	0.8	1.9	
Unadjusted HR (95% CI)	1.00 [ref]	2.21 (0.58–8.45)	0.24
Age and Sex adjusted HR (95% CI)	1.00 [ref]	2.12 (0.56–7.97)	0.26
Model 1: adjusted HR (95% CI)	1.00 [ref]	2.26 (0.63–8.05)	0.20
Model 2: adjusted HR (95% CI)	1.00 [ref]	2.45 (0.63–9.56)	0.19

[1]Data are presented as number or HR (95% CI). An appropriate weight was used for each analysis, except for the number of events and total number. CI = confidence interval; HR = hazard ratio.
[2]Multivariable model 1 was made by adjusting for age (20–39, 40–59, 60–79, 80 y or older), sex (male or female), race and ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and others), educational attainment (more than high school, high school graduation or General Education Development certificate, or less than high school), smoking status (current, former, or never smoker), and body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, and ≥35.0 kg/m^2).
[3]Multivariable Model 2 was made by adjusting for age (20–39, 40–59, 60–79, 80 y or older), sex, race and ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and others), educational attainment (more than high school, high school graduation or General Education Development certificate, or less than high school), smoking status (current, former, or never smoker), body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, and ≥35.0 kg/m^2), hypertension, dyslipidemia, history of cardiovascular disease, and fasting plasma glucose levels (continuous).
[4]Body mass index for multivariable adjustment model 1 and 2 was divided into three groups: <18.5, 18.5–24.9, and 25.0–29.9 kg/m^2.
[5]Body mass index for multivariable adjustment model 1 and 2 was divided into two groups: 30.0–34.9 and ≥35.0 kg/m^2.

Table 4. Risk for cancer mortality in participants who had fasting plasma glucose <100 mg/dl and ≥100 mg/dl with and without hyperinsulinemia[1]

Characteristics	Hyperinsulinemia (−)	Hyperinsulinemia (+)	*p value*
Participants without FPG ≥100 mg/dL			
No. of events/total participants	34/1,375	44/2,134	
Event rate (per 1,000 person-year)	2.3	3.0	
Unadjusted HR (95% CI)	1.00 [ref]	1.26 (0.76–2.11)	0.37
Age and Sex adjusted HR (95% CI)	1.00 [ref]	1.42 (0.85–2.38)	0.17
Model 1: adjusted HR (95% CI)[2]	1.00 [ref]	1.92 (1.07–3.44)	0.02
Model 2: adjusted HR (95% CI)[3]	1.00 [ref]	2.06 (1.12–3.76)	0.02
Participants with FPG <100 mg/dL			
No. of events/total participants	41/4,043	25/2,226	
Event rate (per 1,000 person-year)	0.8	1.6	
Unadjusted HR (95% CI)	1.00 [ref]	1.90 (0.90–4.02)	0.09
Age and sex adjusted HR (95% CI)	1.00 [ref]	2.05 (0.97–4.34)	0.05
Model 1: adjusted HR (95% CI)	1.00 [ref]	1.92 (0.89–4.10)	0.09
Model 2: adjusted HR (95% CI)	1.00 [ref]	1.96 (0.90–4.25)	0.08

[1]Data are presented as number or HR (95% CI). An appropriate weight was used for each analysis, except for the number of events and total number. FPG = fasting plasma glucose; CI = confidence interval; HR = hazard ratio.
[2]Multivariable model 1 was made by adjusting for age (20–39, 40–59, 60–79, 80 y or older), sex (male or female), race and ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and others), educational attainment (more than high school, high school graduation or General Education Development certificate, or less than high school), smoking status (current, former, or never smoker), and body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, and ≥35.0 kg/m^2).
[3]Multivariable Model 2 was made by adjusting for age (20–39, 40–59, 60–79, 80 y or older), sex, race and ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and others), educational attainment (more than high school, high school graduation or General Education Development certificate, or less than high school), smoking status (current, former, or never smoker), body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, and ≥35.0 kg/m^2), hypertension, dyslipidemia, and history of cardiovascular disease.

baseline characteristics were also not significantly associated with cancer death in obese participants. In the model that included the interaction term between hyperinsulinemia and obesity, we found that the association between hyperinsulinemia and cancer mortality was significantly interacted by obesity status (P for interaction term = 0.12). Risk for cancer mortality in participants with and without hyperinsulinemia after multivariable adjustment including physical activity is presented in Supporting Information Table 1. Similar HRs for cancer mortality in nonobese participants were observed after multivariable adjustment including physical activity (adjusted HR 1.98, 95% CI 1.06–3.67, $p = 0.03$). Furthermore, additional sensitivity analyses in nonobese participants limited to the cancer mortality outcome with a follow-up period of at least 1 year showed almost the same results (model 1: HR 1.99, 95% CI 1.12–3.52, $p = 0.01$; model 2: HR 1.95, 95% CI 1.09–3.48, $p = 0.02$) (Table 3). Further analyses in the multivariable model 2 limited to nonobese men, obese men, nonobese women, and obese women were conducted. The HRs for cancer mortality in participants with hyperinsulinemia compared with those without were as follows: HR in nonobese men 1.80, 95% CI 0.96–3.35, $p = 0.06$; HR in obese men 8.04, 95% CI 0.86–75.52, $p = 0.06$: HR in nonobese women 2.30, 95% CI 0.76–6.98, $p = 0.14$; HR in obese women 0.97, 95% CI 0.25–3.79, $p = 0.96$). Although there were limited powers, the HR for cancer mortality was lower in obese women than in the others.

Kaplan–Meier survival curves and event rates for cancer deaths in participants with FPG levels of ≥100 mg/dl and <100 mg/dl are shown in Supporting Information Figure 2 and Table 4, respectively. The cumulative event rates of cancer death in participants with FPG ≥100 mg/dl were significantly higher in those with hyperinsulinemia than in those without (model 1: HR 2.06, 95% CI 1.12–3.44, $p = 0.02$; model 2: HR 2.05, 95% CI 1.12–3.76, $p = 0.02$). In addition, among the participants with FPG levels <100 mg/dl, cancer mortality was higher in those with hyperinsulinemia but not significantly different between those with and without hyperinsulinemia (model 1: HR 1.92, 95% CI 0.89–4.10, $p = 0.09$; model 2: HR 1·96, 95% CI 0.90–4.25, $p = 0.08$). The multivariable adjustments including physical activity did not substantially change these results.

Discussion

To the best of our knowledge, this is the first prospective cohort study using nationally representative data to investigate the association between hyperinsulinemia and cancer mortality in nonobese people. Among nonobese people, hyperinsulinemia was associated with a significantly higher risk of cancer mortality. Furthermore, hyperinsulinemia was also associated with an increased risk of cancer death in people with normal FPG levels.

Insulin resistance is common in people with obesity, metabolic syndrome, and type 2 diabetes; conditions in which hyperinsulinemia is frequently observed. Although these disorders are well

known as risk factors for cardiovascular disease, recent studies have reported that these conditions are also associated with cancer and cancer-related mortality.[23–28] Although the reasons for this association are unclear, hyperinsulinemia may have an important role in tumor initiation and progression.[11,24–29] Hyperinsulinemia may lead to higher risks of cancer development through not only direct mitogenic effects but also through the indirect effect of increased circulating levels of bioavailable insulin-like growth factor 1 (IGF-1).[5,30] IGF-1 has mitogenic and antiapoptotic effects, which can promote cancer proliferation,[31] and some studies have suggested that higher levels of IGF-1 may be associated with an increased risk of cancer and cancer mortality.[30,32] Almost all studies on the association between hyperinsulinemia and cancer have included many obese people and diabetes patients.[24–29] Obesity can lead to adipokine abnormalities, which affect various stages of obesity-induced carcinogenesis.[33] In addition, eating too much of a diet containing carcinogenic compounds may be a risk factor for cancer.[34,35] Moreover, obesity may cause inflammatory responses such as induction of tumor necrosis factor alpha and interleukin 6, leading to promotion of cancer progression.[36] Furthermore, obesity can also result in inferior treatment outcomes and poorer responses to treatment.[37] Thus, obesity is related to many unfavorable factors which cannot be fully statistically adjusted. Similarly, insulin levels in diabetes patients are strongly associated with duration of diabetes and use of antidiabetic medicines. Therefore, we needed to exclude the influence of obesity and diabetes to assess the association between hyperinsulinemia and cancer mortality. Insulin resistance is a heterogeneous disorder that is different in each individual, for which environmental and genetic factors determine susceptibility in varying proportions.[10,11] Therefore, hyperinsulinemia occurs not only in obese people. In the present study, about 30% of nonobese people had hyperinsulinemia. Hyperinsulinemia, regardless of the presence or absence of obesity, may predict a high risk of cancer death. Hyperinsulinemia, regardless of the presence or absence of obesity, may predict a high risk of cancer death. Although hyperinsulinemia in obese women may not be associated with increased risk of cancer death, more large scale studies are required to confirm the results.

A previous study suggested that an increased FPG level might be an independent risk factor for several major cancers,[12] and hyperglycemia has been shown to confer resistance to chemotherapy in breast cancer.[38] A possible explanation is that hyperglycemia-induced oxidative stress leads to cancer progression.[39] Although hyperglycemia and hyperinsulinemia frequently coexist, this study showed that hyperinsulinemia in people with normal FPG levels might be associated with an increased risk of cancer mortality. Further studies are needed to investigate the underlying reasons for these findings.

This study has several limitations. First, there are inherent limitations associated with an observational study design, including possible residual confounding effects from unmeasured covariates. Particularly, the effects of central adiposity may not be fully adjusted even with multiple analyses including BMI and waist circumference. Second, this was a short-term follow-up study. In addition, because the nonobese participants without diabetes or a history of cancer had low mortality risks, the relatively small number of events may have influenced the results. Although various analyses indicate the findings in this study were robust, a longer-term and larger-scale study is needed to confirm the results. Third, the HRs for cancer death in participants with hyperinsulinemia varied among assays for insulin measurement. Further studies are needed to clarify the association between the risk of cancer death and fasting insulin levels measured by standardized assays. Fourth, the outcome of the present study was cancer mortality, but cancer development was not assessed. Therefore, we could not tell whether the cancer mortality in nonobese people with hyperinsulinemia was attributable to cancer development or accelerated growth of cancer after development. Moreover, the types of cancer were not known. To reveal the pathophysiological relationship between hyperinsulinemia and cancer death, further studies are required. However, our findings may have a significant impact on the prevention of serious and advanced cancers, leading to decreased risks of cancer death.

In conclusion, this study showed that nonobese people with hyperinsulinemia had a higher risk of cancer mortality. Even if people are not obese, improvement of hyperinsulinemia by increased physical activity and avoidance of a sedentary lifestyle may be an important approach for preventing cancer.

Author Contributions

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Analysis and interpretation of data: Tetsuro Tsujimoto and Takehiro Sugiyama

Drafting of the manuscript: Tetsuro Tsujimoto, Hiroshi Kajio, and Takehiro Sugiyama

Statistical analysis: Tetsuro Tsujimoto and Takehiro Sugiyama

Dr. Tsujimoto had full access to all of the data in the study and takes responsibility for the integrity and accuracy of data analysis.

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