Cancer Causes Control (2017) 28:625–633
DOI 10.1007/s10552-017-0884-0

ORIGINAL PAPER

Fasting but not casual blood glucose is associated with pancreatic cancer mortality in Japanese: EPOCH-JAPAN

Masato Nagai[1,2] · Yoshitaka Murakami[3] · Akiko Tamakoshi[4] · Yutaka Kiyohara[5] · Michiko Yamada[6] · Shigekazu Ukawa[4] · Takumi Hirata[7] · Sachiko Tanaka[8] · Katsuyuki Miura[9,10] · Hirotsugu Ueshima[9,10] · Tomonori Okamura[11] · Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) Research Group

Received: 1 September 2016 / Accepted: 11 March 2017 / Published online: 28 March 2017

Abstract
Purpose The dose–response relationship between fasting blood glucose levels and risk of pancreatic cancer has been investigated, but the association between casual blood glucose levels and pancreatic cancer death has not been examined. We examined the association between casual and fasting blood glucose levels and death due to pancreatic cancer in Japanese.
Methods We performed a pooled analysis of the individual Japanese including 46,387 participants aged 40–79 years from ten cohorts. Participants were classified into five groups: low normal, middle normal, high normal, prediabetes (casual blood glucose 140–199 mg/dl, or fasting blood glucose 110–125 mg/dl), and diabetes (casual blood glucose ≥200 mg/dl, fasting blood glucose ≥126 mg/dl, or anti-diabetic drug use). Low normal, middle normal, and high normal were defined according to tertiles of casual or fasting normal blood glucose levels. Hazard ratios (HRs) and 95% confidence intervals (CIs) for pancreatic cancer mortality were estimated stratifying casual and fasting blood glucose by cohort-stratified Cox proportional hazards regression analysis, with low normal (casual blood glucose <94 mg/dl, or fasting blood glucose <90 mg/dl) as a reference.
Results Fasting blood glucose showed a dose–response relationship with pancreatic cancer mortality (p for trend = 0.005). After adjusting for covariates, HRs (95% CIs) were 2.83 (1.18–6.76) for prediabetes and 3.96 (1.56–10.08) for diabetes. However, there were no significant associations with casual blood glucose. These tendencies were observed after the exclusion of participants who were censored for the first 5 years of follow-up.
Conclusions Fasting blood glucose is a better predictor of pancreatic cancer death than casual blood glucose.

Keywords Blood glucose · EPOCH-JAPAN · Japanese · Pancreatic cancer · Meta-analysis

Electronic supplementary material The online version of this article (doi:10.1007/s10552-017-0884-0) contains supplementary material, which is available to authorized users.

✉ Masato Nagai
m-nagai@med.tohoku.ac.jp

1 Tohoku Medical Megabank Organization, Tohoku University, 2-1 Seiryo-machi, Aoba-ku, Sendai 980-8573, Japan

2 Graduate School of Medicine, Tohoku University, Sendai, Japan

3 Department of Medical Statistics, Toho University School of Medicine, Tokyo, Japan

4 Department of Public Health Sciences, Hokkaido University Graduate School of Medicine, Sapporo, Japan

5 Departments of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

6 Department of Clinical Studies, Radiation Effects Research Foundation, Hiroshima, Japan

7 Center for Supercentenarian Medical Research, Keio University School of Medicine, Tokyo, Japan

8 Department of Medical Statistics, Shiga University of Medical Science, Otsu, Japan

9 Department of Public Health, Shiga University of Medical Science, Otsu, Japan

10 Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Otsu, Japan

11 Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo, Japan

Abbreviations

EPOCH-JAPAN	Evidence for Cardiovascular Prevention from Observational Cohorts in Japan
BMI	Body mass index
ICD	The International Classification of Diseases and Related Health Problems
HR	Hazard ratio
CI	Confidence interval
ANOVA	Analysis of variance
SD	Standard deviation.

Introduction

Pancreatic cancer is one of the most fatal cancers [1], and the ninth most common cause of cancer deaths worldwide [1]. Although pancreatic cancer is rare in Asia (age-adjusted rate <1/100,000) compared with Western countries (age-adjusted rate 10–15/100,000), its incidence is higher in some high-income countries such as Japan (age-adjusted rate in 2011 8.7/100,000), similar to Western countries [1, 2]. Pancreatic cancer is the fourth most common cause of cancer death in Japan [3]. This tendency is similar to that in other developed countries [4]. It accounted for 8.4% of all cancer deaths in 2013 [3], with a 5-year relative survival rate of 7.0% in participants diagnosed in 2003–2005 in Japan [5].

Previous studies have shown a clear association between diabetes and an increased risk of pancreatic cancer [6–9]. Furthermore, a linear dose–response relationship between fasting blood glucose levels and pancreatic cancer risk has been reported in a meta-analysis [10]. A similar relationship was observed in Asian populations in a pooled analysis including Japanese and Korean cohorts [11, 12]. However, insulin sensitivity and insulin response differ among East Asians, Caucasians, and Africans [13], and the impact of obesity on diabetes is consequently also different among Asian, White, Hispanic, and Black populations [14]. Raimondi et al. noted that the incidence of pancreatic cancer varied greatly between regions because of differences in lifestyle factors such as diet, or environmental factors such as vitamin D exposure [4]. The relationships among diabetes, blood glucose level, and pancreatic cancer might thus be different in Japanese individuals. Although the impact of diabetes on pancreatic cancer risk has also been observed in Japanese individuals [8, 9], the dose–response relationship between fasting blood glucose levels and pancreatic cancer mortality and incidence has not been investigated.

A systematic review reported an association between glycosylated hemoglobin (HbA1c) and pancreatic cancer [15]. It is therefore possible that casual blood glucose levels, as well as fasting levels, may also be associated with pancreatic cancer, because HbA1c is associated with 24 h mean blood glucose [16]. However, such an association between casual blood glucose levels and pancreatic cancer has not been examined.

The purpose of this study was to examine the association between casual and fasting blood glucose levels and death due to pancreatic cancer in Japanese individuals, based on a large pooled analysis, including well-established cohorts enrolled in the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN).

Materials and methods

Study population

The EPOCH-JAPAN database has been described in detail elsewhere [17]. Briefly, EPOCH-JAPAN is a pooling project for several well-qualified cohort studies in Japanese individuals. The database examining cancer deaths includes 12 cohorts (Tanno–Sobetsu, Ohsaki, Ohasama, Oyabe, YKK workers, Suita, RERF cohort, Hisayama, JACC, NIPPON DATA80, NIPPON DATA90, and Osaka), with a total of 99,951 participants.

We excluded two cohorts (Oyabe and JACC; 35,462 participants) because information of blood glucose was not pooled in the database. Additional exclusions were made in the case of participants who were aged <40 or ≥80 years ($n=12{,}000$), had a reported history of cancer ($n=616$), or had missing information about blood glucose ($n=5{,}486$). A total of 46,387 participants (20,426 men and 25,961 women) were finally included in the study analysis.

Blood glucose level

Blood glucose levels were measured in the plasma in all but two cohorts (RERF and Osaka cohorts), in which they were measured in the serum. Blood collection time was pooled as dichotomous variable (fasting or not). If information on blood collection time was not fasting or missing, we treated the blood glucose level as casual.

Endpoint

In accordance with Family Registration Law in Japan, all death certificates are forwarded to the Ministry of Health, Labour and Welfare via the public health center in the area of residence [18]. Registration of death is required and completed by law. Some studies have used other sources, such as autopsy reports [19, 20], medical records [19–21], health examinations [21, 22], and questionnaires. The underlying causes of death were coded according to the International Classification of Diseases and Related Health Problems, the Ninth Revision (ICD-9) until the end of

1994, and the Tenth Revision (ICD-10) from the beginning of 1995 [23, 24]. Pancreatic cancer deaths were defined by codes 157 or C25.

Person-years of follow-up were counted for each participant, until the date of pancreatic cancer death, withdrawal from each cohort, or the end of the study period, whichever occurred first.

Statistical analysis

Participants were classified into three groups according to blood glucose level and anti-diabetic drug use: normal (casual blood glucose level <140 mg/dl, or fasting blood glucose level <110 mg/dl), prediabetes (casual blood glucose level 140–199 mg/dl, or fasting blood glucose level 110–125 mg/dl), and diabetes (casual blood glucose level ≥200 mg/dl, fasting blood glucose level ≥126, or anti-diabetic drug use) [25]. HbA1c was not included in the definition of diabetes because its information was not pooled in the database. Participants in the normal category were further divided in tertiles: low normal (casual blood glucose level <94 mg/dl, or fasting blood glucose level <90 mg/dl), middle normal (casual blood glucose level 94–107 mg/dl, or fasting blood glucose level 90–96 mg/dl), and high normal (casual blood glucose level 108–139 mg/dl, or fasting blood glucose level 97–109 mg/dl). Participants were thus classified into five groups in the present study.

Hazard ratios (HRs) and 95% confidence intervals (CIs) for pancreatic cancer mortality were estimated after stratifying casual and fasting blood glucose levels by cohort-stratified Cox proportional hazards regression analysis, which accounted for the variability in baseline hazards among cohorts, with low normal as a reference. The following variables were considered to be potential confounding factors in multi-adjusted 1: sex, age (continuous variable), body mass index (BMI) (<18.5, 18.5 to <25.0, and ≥25.0 kg/m^2), cigarette smoking (never smoker, past smoker, and current smoker), and alcohol drinking (never drinker, past drinker, and current drinker). Tests for trends were calculated from categorical variable (ordinal scale). In addition, the analyses were repeated after excluding 2,950 participants (pancreatic cancer death $n=61$) who were censored for the first 5 years after each baseline survey in multi-adjusted 2.

As a source of potential interaction, analyses were repeated after stratifying by sex, age (<65 or ≥65 years), BMI (<25.0 or ≥25.0 kg/m^2), cigarette smoking (never smoker, or past, or current smoker), and alcohol drinking (never drinker, or past, or current drinker).

Statistical analyses were conducted using SAS software (version 9.3, Cary, NC, USA). All hypothesis tests were two-sided and based on a level of significance of 0.05.

Results

The characteristics of the ten cohorts are shown in Table 1. Each baseline survey was performed between 1977 and 1994, with the number of participants ranging from 791 in Ohasama to 12,789 in Ohsaki. The mean (standard deviation) follow-up period of the overall study population was 14.6 (±5.6) years, ranging from 11.1 years in Ohsaki to 23.0 years in Tanno–Sobetsu. There were 258 pancreatic cancer deaths during 678,001.0 person-years of follow-up.

The baseline characteristics of the study participants according to blood glucose level are shown in Tables 2 and 3. Compared with low normal, participants in the diabetes group were older and more prevalent of men,

Table 1 Characteristics of the cohort studies

	n	Baseline years	Women (%)	Mean follow-up (SD[a])	Person-years	Mean age (SD)	Pancreatic cancer deaths	Mortality[b]
All	46,387	1977–1994	56.0	14.6 (5.6)	678,001.0	57.7 (10.4)	258	38.1
Tanno–Sobetsu	1,808	1977	53.4	23.0 (7.6)	41,637.4	50.7 (7.0)	12	28.8
Ohsaki	12,789	1994	56.8	11.1 (3.6)	141,831.3	61.9 (9.2)	48	33.8
Ohasama	791	1987	65.9	12.7 (3.2)	10,039.2	58.5 (8.9)	7	69.7
YKK	2,975	1990	34.5	18.5 (5.1)	54,942.4	47.3 (5.4)	5	9.1
Suita	5,373	1989	51.9	13.6 (3.6)	73,196.6	59.2 (10.8)	45	61.5
RERF cohort	2,199	1986	67.6	17.8 (5.1)	39,122.9	59.0 (10.4)	19	48.6
Hisayama	2,556	1988	57.1	12.9 (2.9)	32,889.4	57.8 (10.5)	10	30.4
ND80	6,911	1980	55.9	20.4 (6.1)	140,835.2	55.7 (10.2)	58	41.2
ND90	5,731	1990	57.0	13.9 (3.0)	79,418.2	56.5 (10.7)	32	40.3
Osaka	5,254	1985	63.3	12.2 (2.5)	64,088.4	57.8 (9.7)	22	34.3

[a] *SD* standard deviation

[b] Mortality: /100,000 person-years

Table 2 Baseline distribution of the study participants according to casual blood glucose level

	Low normal (<94 mg/dl)	Middle normal (94–107 mg/dl)	High normal (108–139 mg/dl)	Prediabetes (140–199 mg/dl)	Diabetes (≥200 mg/dl)	*p* value[b]
No. of participants	8,556	9,126	9,189	2,775	1,676	
Women (%)	61.8	59.5	56.4	52.6	51.7	<0.0001
Mean age (years) (SD[a])	57.5 (10.2)	59.4 (10.1)	58.8 (10.5)	60.1 (10.2)	63.2 (8.8)	<0.0001
BMI[a] (%)						
<18.5 kg/m^2	4.9	4.2	4.8	5.7	4.6	<0.0001
18.5 to <25.0 kg/m^2	69.8	64.4	64.7	63.3	64.6	
≥25.0 kg/m^2	25.2	31.4	30.5	31.1	30.8	
Cigarette smoking (%)						
Never	62.0	61.1	60.1	55.3	54.2	<0.0001
Past	10.9	13.4	12.4	11.8	14.4	
Current	27.1	25.5	27.5	32.9	31.4	
Alcohol consumption (%)						
Never	56.9	53.6	53.6	53.5	50.5	<0.0001
Past	3.8	3.9	4.1	4.2	6.3	
Current	39.2	42.6	42.3	42.3	43.2	

[a] *SD* standard deviation, *BMI* body mass index

[b] *p* values were calculated by chi-squared test (categorical variables), or ANOVA (continuous variables)

Table 3 Baseline distribution of the study participants according to fasting blood glucose level

	Low normal (<90 mg/dl)	Middle normal (90–96 mg/dl)	High normal (97–109 mg/dl)	Prediabetes (110–125 mg/dl)	Diabetes (≥126 mg/dl)	*p* value[c]
No. of participants	4163	4298	4670	1195	739	
Women (%)	59.1	54.6	46.1	39.8	40.1	<0.0001
Mean age (years) (SD[a])	52.2 (9.5)	55.0 (10.4)	56.6 (10.2)	58.5 (10.3)	59.2 (9.5)	<0.0001
BMI[a] (%)						
<18.5 kg/m^2	6.7	5.7	4.8	4.1	3.5	<0.0001
18.5 to <25.0 kg/m^2	77.4	73.2	69.1	63.1	62.4	
≥25.0 kg/m^2	15.9	21.2	26.1	32.8	34.1	
Cigarette smoking (%)						
Never	61.7	59.4	54.1	48.9	47.8	<0.0001
Past	7.2	11.7	17.7	17.9	19.6	
Current	31.1	28.9	28.2	33.2	32.6	
Alcohol consumption (%)						
Never	56.9	53.4	49.0	44.7	44.5	<0.0001
Past	1.8	2.9	2.9	2.8	4.3	
Current	41.4	43.7	48.1	52.6	51.2	

[a] *SD* standard deviation, *BMI* body mass index

[b] *p* values were calculated by chi-squared test (categorical variables), or ANOVA (continuous variables)

BMI ≥25.0 kg/m^2, past smokers, past drinkers, and current drinkers regardless of blood collection times. Current smokers were more prevalent according to only fasting blood glucose.

Tables 4 and 5 show person-year totals, number of pancreatic cancer deaths, and HRs of pancreatic cancer mortality with 95% CIs according to casual and fasting blood glucose levels. In multi-adjusted analysis, compared with low normal, pancreatic cancer mortality increased significantly with increasing fasting blood glucose levels, though no similar significant association was observed for casual blood glucose levels. In multi-adjusted 1, the HRs for pancreatic cancer mortality according to casual blood glucose were 1.40 (95% CI 0.78–2.52) for prediabetes and 1.63

Table 4 Hazard ratios and 95% confidence intervals of pancreatic cancer mortality according to casual blood glucose level

	Low normal (<94 mg/dl)	Middle normal (94–107 mg/dl)	High normal (108–139 mg/dl)	Prediabetes (140–199 mg/dl)	Diabetes (≥200 mg/dl)	*p* for trend[c]
Men and women						
No. of participants	8,556	9,126	9,189	2,775	1,676	
Person-years	111,531.7	120,757.6	146,798.9	44,839.3	22,093.7	
No. of pancreatic cancer deaths	35	56	51	25	15	
Crude	Reference	1.47(0.96–2.25)	1.13(0.70–1.82)	1.85(1.05–3.28)	2.17(1.17–4.02)	0.016
Age-sex-adjusted	Reference	1.33(0.87–2.03)	0.93(0.58–1.50)	1.33(0.75–2.36)	1.50(0.81–2.79)	0.334
Multi-adjusted 1[a]	Reference	1.32(0.85–2.06)	0.95(0.58–1.56)	1.40(0.78–2.52)	1.63(0.87–3.05)	0.202
Multi-adjusted 2[b]	Reference	1.33(0.75–2.36)	0.92(0.52–1.62)	1.33(0.69–2.57)	1.51(0.73–3.13)	0.254
Men						
No. of participants	3,267	3,692	4,009	1,315	810	
Person-years	41,522.5	48,131.8	61,744.1	19,665.5	9,855.8	
No. of pancreatic cancer deaths	21	29	28	16	12	
Multi-adjusted 1	Reference	1.10(0.61–1.96)	0.74(0.40–1.40)	1.22(0.59–2.51)	1.84(0.88–3.84)	0.209
Multi-adjusted 2	Reference	0.89(0.43–1.82)	0.66(0.31–1.42)	1.14(0.49–2.66)	1.70(0.69–4.14)	0.299
Women						
No. of participants	5,289	5,434	5,180	1,460	866	
Person-years	70,009.2	72,625.8	85,054.8	25,173.7	12,237.8	
No. of pancreatic cancer deaths	14	27	23	9	3	
Multi-adjusted 1	Reference	1.68(0.83–3.40)	1.37(0.62–3.05)	1.82(0.68–4.88)	1.02(0.28–3.72)	0.651
Multi-adjusted 2	Reference	1.27(0.58–2.75)	1.32(0.57–3.09)	1.58(0.55–4.54)	1.10(0.30–4.05)	0.607

[a]Multi-adjusted 1 was adjusted for sex, age (continuous), body mass index (<18.5 kg/m^2, 18.5 to <25.0 kg/m^2, or ≥25.0 kg/m^2), cigarette smoking (never, past, or current), and alcohol consumption (never, past, or current)

[b]Multi-adjusted 2 excluded from multi-adjusted 1 the 1,051 men and 1,207 women where censored for the first 5 years after baseline (number of pancreatic cancer deaths: 31 men and 12 women)

[c]*p* for trend was calculated as a categorical variable (ordinal scale)

(0.87–3.05) for diabetes (*p* for trend = 0.202). The corresponding values for fasting blood glucose level were 2.83 (1.18–6.76) for prediabetes and 3.96 (1.56–10.08) diabetes (*p* for trend = 0.005). Similar non-significant and significant associations were observed in multi-adjusted two after exclusion of participants who were censored for the first 5 years of follow-up. After stratification according to sex, prediabetes and diabetes were associated with pancreatic cancer mortality in men, but there was no association between either elevated casual or fasting blood glucose levels in pancreatic cancer in women.

We observed similar tendencies between blood glucose level and pancreatic cancer mortality in multi-adjusted 2 after stratification by age, BMI, smoking, and drinking (Supplemental Tables 1 and 2). All the above-stratified analyses showed non-significant interactions for casual and fasting blood glucose.

Discussion

The results of the present study revealed a dose–response relationship between fasting blood glucose levels and pancreatic cancer mortality, but no such association between casual blood glucose levels and pancreatic cancer mortality. The risk of pancreatic cancer mortality was particularly increased in individuals with not only diabetes but also prediabetes according to fasting blood glucose levels. This was the first study to investigate the risk of pancreatic cancer death according to fasting blood glucose levels in Japanese individuals, who have a unique dietary pattern [26–28] and casual blood glucose levels in the world.

Present study showed a dose–response relationship between fasting blood glucose levels and pancreatic cancer risk in Japanese individuals that was in accordance with a previous meta-analysis [10]. In general, various metabolic and hormonal factors related to glucose metabolism, including hyperglycemia, insulin resistance, and hyperinsulinemia, are proposed to be involved in the mechanisms underlying the onset of cancer [7, 8, 29, 30]. For example, hyperglycemia provides more glucose and induces pancreatic cancer cell growth [7, 29, 30], and is also associated with increased free radical formation, and may lead to the development of advanced glycation end products that can increase inflammation [31]. In addition, insulin resistance promotes the overproduction of reactive oxygen species

Table 5 Hazard ratios and 95% confidence intervals of pancreatic cancer mortality according to fasting blood glucose level

	Low normal (<90 mg/dl)	Middle normal (90–96 mg/dl)	High normal (97–109 mg/dl)	Prediabetes (110–125 mg/dl)	Diabetes (≥126 mg/dl)	*p* for trend[c]
Men and women						
No. of participants	4,163	4,298	4,670	1,195	739	
Person-years	69,777.7	66,606.8	69,076.4	16,763.1	9,755.9	
No. of pancreatic cancer deaths	11	23	21	12	9	
Crude	Reference	1.94(0.94–3.99)	1.64(0.78–3.43)	3.92(1.71–9.00)	5.18(2.11–12.69)	<0.001
Age-sex-adjusted	Reference	1.73(0.84–3.59)	1.30(0.61–2.74)	2.61(1.13–6.07)	3.57(1.44–8.84)	0.010
Multi-adjusted 1[a]	Reference	1.82(0.85–3.88)	1.47(0.67–3.19)	2.83(1.18–6.76)	3.96(1.56–10.08)	0.005
Multi-adjusted 2[b]	Reference	1.82(0.77–4.27)	1.24(0.51–3.05)	3.21(1.24–8.33)	3.34(1.11–10.05)	0.021
Men						
No. of participants	1,704	1,950	2,517	719	443	
Person-years	29,237.3	30,535.7	36,994.8	10,138.1	5,791.1	
No. of pancreatic cancer deaths	6	13	14	10	7	
Multi-adjusted 1	Reference	1.84(0.64–5.29)	1.63(0.57–4.65)	3.63(1.19–11.08)	4.73(1.44–15.50)	0.004
Multi-adjusted 2	Reference	1.76(0.53–5.85)	1.15(0.33–3.95)	4.32(1.28–14.60)	5.05(1.35–18.91)	0.003
Women						
No. of participants	2,459	2,348	2,153	476	296	
Person-years	40,540.4	36,071.1	32,081.7	6,625.0	3,964.8	
No. of pancreatic cancer deaths	5	10	7	2	2	
Multi-adjusted 1	Reference	1.76(0.59–5.24)	1.38(0.43–4.46)	1.32(0.25–7.04)	2.97(0.55–16.12)	0.429
Multi-adjusted 2	Reference	1.92(0.56–6.55)	1.46(0.40–5.37)	0.83(0.09–7.75)	–	0.723

[a]Multi-adjusted 1 was adjusted for sex, age (continuous), body mass index (<18.5 kg/m^2, 18.5-<25.0 kg/m^2, or ≥25.0 kg/m^2), cigarette smoking (never, past, or current), and alcohol consumption (never, past, or current)

[b]Multi-adjusted 2 excluded from multi-adjusted 1 the 395 men and 229 women where censered for the first 5 years after baseline (number of pancreatic cancer deaths: 11 men and 7 women)

[c]P for trend was calculated as a categorical variable (ordinal scale)

[32, 33]. Chronic inflammation and oxidative stress caused by hyperglycemia or insulin resistance are known to cause DNA damage and are linked to the development of cancer [33, 34]. Although these mechanisms are not organ-specific in pancreatic cancer [33, 35], it has been suggested that hyperglycemia and insulin resistance may play important roles in the development of pancreatic cancer. Fasting blood glucose levels were positively associated with insulin resistance in diabetic and non-diabetic participants [36], which is in accordance with the current results. Our results suggested that the risk of pancreatic cancer death increased notably from a condition of prediabetes assessed by fasting blood glucose levels.

In contrast, there was no association between casual blood glucose and pancreatic cancer mortality. Casual blood glucose levels differ markedly depending on the measurement time after eating. Glucose levels measured at unknown times were defined as casual blood glucose levels in the present study, and these non-differential misclassifications will weaken any true association toward the null and induce the no association. Alternatively, previous reports showed that fasting blood glucose levels were associated with hepatic insulin resistance, while postprandial blood glucose levels were mainly linked to insulin resistance in skeletal muscle [37, 38]. Our results suggest that hepatic insulin resistance, not insulin resistance in skeletal muscle, may be an important factor in the pancreatic cancer development. Furthermore, blood glucose elevations during fasting, or whole day rather than transient postprandial hyperglycemia, might also increase the risk of pancreatic cancer given that HbA1c levels, as an index of 24 h mean blood glucose, were shown to be associated with pancreatic cancer in a previous report [15].

Stratification by sex showed that the above associations only occurred in men. However, Jee et al. showed that fasting blood glucose levels were associated with pancreatic cancer risk in both men and women [12]. It is possible that the lack of any association between fasting blood glucose levels and pancreatic cancer mortality in women in the current study was the result of the small number of events.

Notably, there were only two pancreatic cancer deaths in women in the prediabetes and diabetes fasting blood glucose groups, respectively, and no pancreatic cancer deaths in the diabetes group after exclusion of a participant who was censored for the first 5 years after baseline. We conducted additional stratified analyses to examine the interactions with age, BMI, smoking, and drinking. Obesity is associated with both metabolic disorders and pancreatic cancer death [1, 39]. However, even though Lin et al. showed a significant increase in the risk of pancreatic cancer death in only underweight individuals with a history of diabetes, there was no interaction between BMI ≥18.5 kg/m^2 and history of diabetes on pancreatic cancer in Asians (p for interaction = 0.07) [40]. In the present study, the association between blood glucose level and pancreatic cancer deaths was not modified by BMI <25 kg/m^2 or ≥25 kg/m^2. Meanwhile, never smokers and never drinkers showed no association between fasting blood glucose levels and pancreatic cancer mortality. The prevalence of women in whom fasting blood glucose level was not associated with pancreatic cancer mortality was higher in these strata.

This study had some limitations. First, information on the history of cancer was only pooled in a few cohorts, and it is possible that the present results were affected by individuals' cancer history. However, we conducted analyses excluding participants who were censored for the first 5 years after each baseline, and the observed association was robust. We considered that the possible effect of reverse causation, whereby raised blood glucose levels could be due to a history of pancreatic cancer or undiagnosed pancreatic cancer, would be eliminated because of the very low 5-year survival of pancreatic cancer [1]. After exclusion, most analyzed participants would not have any history of pancreatic cancer, or any undiagnosed pancreatic cancer at each baseline. Second, blood glucose was measured at the beginning of the follow-up period. The distribution of single baseline glucose measures is therefore wider than the distribution of true usual glucose values because of regression to the mean, resulting in potential regression dilution bias [41]. This bias weakens any true association towards the null. Participants might have been reclassified when they were examined during the follow-up period, and this bias may have masked any association between casual blood glucose levels and pancreatic cancer mortality. Third, we observed few pancreatic cancer deaths in women in the prediabetes and diabetes, respectively, therefore the statistical model and result of women in stratified analysis might be instable.

In conclusion, fasting, but not casual blood glucose levels showed a linear association with the risk of pancreatic cancer death in Japanese individuals. The risks of pancreatic cancer mortality were particularly significantly increased in individuals with prediabetes and diabetes according to fasting blood glucose levels. The detailed mechanisms responsible for the different impacts of casual and fasting blood glucose on pancreatic cancer remain unknown, but fasting blood glucose appears to be a more reliable predictive index of pancreatic cancer death than casual blood glucose.

Acknowledgements We are grateful to all the participants in each cohort study. We thank Mrs. Toshimi Yoshida (Shiga University of Medical Science) and Mrs. Satoko Narikawa (Keio University) for expert clerical assistance.

Author contributions HU, TO, and KM conceived and designed the pooling project. YM constructed the EPOCH-JAPAN database. MN and AT contributed to the design of the study. MN, YM, and ST participated in data analysis. MN and AT participated in the writing of the manuscript. All authors participated in the critical revision of the manuscript and approved the final version of the report for submission.

Funding This research was supported by a grant–in–aid from the Ministry of Health, Labour and Welfare, Health and Labor Sciences research grants, Japan (Research on Health Services: H17–Kenkou–007; Comprehensive Research on Cardiovascular Disease and Life–Related Disease: H18–Junkankitou[Seishuu]–Ippan–012; Comprehensive Research on Cardiovascular Disease and Life–Related Disease: H19–Junkankitou [Seishuu]–Ippan–012; Comprehensive Research on Cardiovascular and Life–Style Related Diseases: H20–Junkankitou [Seishuu]–Ippan–013; Comprehensive Research on Cardiovascular and Life–Style Related Diseases: H23–Junkankitou [Seishuu]–Ippan–005); an Intramural Research Fund (22-4-5) for Cardiovascular Diseases of National Cerebral and Cardiovascular Center; and Comprehensive Research on Cardiovascular and Life-Style Related Diseases (H26-Junkankitou [Seisaku]-Ippan-001).

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest associated with this manuscript.

Appendix

The Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH–JAPAN) Research Group is composed of the following investigators. Chairperson: Hirotsugu Ueshima (Shiga University of Medical Science); Co–Chairperson: Tomonori Okamura (Keio University);

Executive committee: Hirotsugu Ueshima (Shiga University of Medical Science), Yutaka Imai (Tohoku University Graduate School of Pharmaceutical Sciences), Takayoshi Ohkubo (Teikyo University School of Medicine), Fujiko Irie (Ibaraki Prefecture), Hiroyasu Iso, Akihiko Kitamura (Osaka University Graduate School of Medicine), Yutaka Kiyohara (Kyushu University Graduate School of Medicine), Katsuyuki Miura (Shiga University of Medical Science), Yoshitaka Murakami (Toho University), Hideaki Nakagawa (Kanazawa Medical University),

Takeo Nakayama (Kyoto University School of Public Health), Akira Okayama (Research Institute of Strategy for Prevention), Toshimi Sairenchi (Dokkyo Medical University), Shigeyuki Saitoh (Sapporo Medical University), Kiyomi Sakata (Iwate Medical University), Akiko Tamakoshi (Hokkaido University Graduate School of Medicine), Ichiro Tsuji (Tohoku University Graduate School of Medicine), Michiko Yamada (Radiation Effects Research Foundation), Masahiko Kiyama (Osaka Center for Cancer and Cardiovascular Disease Prevention), Yoshihiro Miyamoto (National Cerebral and Cardiovascular Center), Shizukiyo Ishikawa (Jichi Medical University), Hiroshi Yatsuya (Fujita Health University), and Tomonori Okamura (Keio University School of Medicine).

References

1. World Cancer Research Fund/American Institute for Cancer Research (2007) Food, nutrition, physical activity, and the prevention of cancer: a global perspective. AICR, Washington, DC
2. Cancer Information Service, National Cancer Center, Japan. http://ganjoho.jp/en/professional/statistics/table_download.html. Accessed 6 June 2016
3. Statistics and Information Department Minister's Secretariat, Ministry of Health, Labour and Welfare of Japan (2015) Vital statistics of Japan 2013. Health, Labour and Welfare Statistics Association, Tokyo
4. Raimondi S, Maisonneuve P, Lowenfels AB (2009) Epidemiology of pancreatic cancer: an overview. Nat Rev Gastroenterol Hepatol 6:699–708
5. Monitoring of Cancer Incidence in Japan-Survival 2003–2005 Report (Center for Cancer Control and Information Services, National Cancer Center, 2013). http://ganjoho.jp/en/professional/statistics/table_download.html. Accessed 6 June 2016
6. Ben Q, Xu M, Ning X et al (2011) Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. Eur J Cancer 47:1928–1937
7. Giovannucci E, Harlan DM, Archer MC et al (2010) Diabetes and cancer: a consensus report. Diabetes Care 33:1674–1685
8. Kasuga M, Ueki K, Tajima N et al (2013) Report of the Japan Diabetes Society/Japanese Cancer Association Joint Committee on Diabetes and Cancer. Cancer Sci 104:965–976
9. Sasazuki S, Charvat H, Hara A et al (2013) Diabetes mellitus and cancer risk: pooled analysis of eight cohort studies in Japan. Cancer Sci 104:1499–1507
10. Liao WC, Tu YK, Wu MS, Lin JT, Wang HP, Chien KL (2015) Blood glucose concentration and risk of pancreatic cancer: systematic review and dose-response meta-analysis. BMJ 349:g7371
11. Ansary-Moghaddam A, Huxley R, Barzi F, et al (2006) The effect of modifiable risk factors on pancreatic cancer mortality in populations of the Asia-Pacific region. Cancer Epidemiol Biomark Prev 15:2435–2440
12. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM (2005) Fasting serum glucose level and cancer risk in Korean men and women. JAMA 293:194–202
13. Kodama K, Tojjar D, Yamada S, Toda K, Patel CJ, Butte AJ (2013) Ethnic differences in the relationship between insulin sensitivity and insulin response: a systematic review and meta-analysis. Diabetes Care 36:1789–1796
14. Shai I, Jiang R, Manson JE et al (2006) Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. Diabetes Care 29:1585–1590
15. Hope C, Robertshaw A, Cheung KL, Idris I, English E (2015) Relationship between HbA1c and cancer in people with or without diabetes: a systematic review. Diabetes Med. doi:10.1111/dme.13031
16. Zhou J, Mo Y, Li H et al (2013) Relationship between HbA1c and continuous glucose monitoring in Chinese population: a multicenter study. PLoS ONE 8:e83827
17. Murakami Y, Hozawa A, Okamura T, Ueshima H (2008) Relation of blood pressure and all-cause mortality in 180,000 Japanese participants: pooled analysis of 13 cohort studies. Hypertension 51:1483–1491
18. The Ministry of Health Labour and Welfare (2016) Mannual to fill in a death certificate (in Japanese). The Ministry of Health, Labour, and Welfare. http://www.mhlw.go.jp/toukei/manual/. Accessed 6 June 2016
19. Mannami T, Konishi M, Baba S, Nishi N, Terao A (1997) Prevalence of asymptomatic carotid atherosclerotic lesions detected by high-resolution ultrasonography and its relation to cardiovascular risk factors in the general population of a Japanese city: the Suita study. Stroke 28:518–525
20. Arima H, Tanizaki Y, Kiyohara Y et al (2003) Validity of the JNC VI recommendations for the management of hypertension in a general population of Japanese elderly: the Hisayama study. Arch Intern Med 163:361–366
21. Ohkubo T, Kikuya M, Metoki H et al (2005) Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. J Am Coll Cardiol 46:508–515
22. Kuriyama S, Shimazu T, Ohmori K et al (2006) Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. JAMA 296:1255–1265
23. World Health Organization (1977) Manual of the international statistical classification of diseases, injuries, and causes of death. 9th rev. WHO, Geneva
24. World Health Organization (1992) International statistical classification of diseases and related health problems, 10th edn. WHO, Geneva
25. American Diabetes Association (2015) Classification and diagnosis of diabetes. Diabetes Care 38:S8–S16
26. Tada N, Maruyama C, Koba S et al (2011) Japanese dietary lifestyle and cardiovascular disease. J Atheroscler Thromb 18:723–734
27. Brown IJ, Tzoulaki I, Candeias V, Elliott P (2009) Salt intakes around the world: implications for public health. Int J Epidemiol 38:791–813
28. Zhou BF, Stamler J, Dennis B et al (2003) Nutrient intakes of middle-aged men and women in China, Japan, United Kingdom, and United States in the late 1990s: the INTERMAP study. J Hum Hypertens 17:623–630
29. Regel I, Kong B, Raulefs S et al (2012) Energy metabolism and proliferation in pancreatic carcinogenesis. Langenbecks Arch Surg 397:507–512
30. Chaika NV, Yu F, Purohit V et al (2012) Differential expression of metabolic genes in tumor and stromal components of primary and metastatic loci in pancreatic adenocarcinoma. PLoS ONE 7:e32996
31. Grote VA, Rohrmann S, Nieters A et al (2011) Diabetes mellitus, glycated haemoglobin and C-peptide levels in relation to pancreatic cancer risk: a study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Diabetologia 54:3037–3046

32. Chang YC, Chuang LM (2010) The role of oxidative stress in the pathogenesis of type 2 diabetes: from molecular mechanism to clinical implication. Am J Transl Res 2:316–331
33. Biadgo B, Abebe M (2016) Type 2 diabetes mellitus and its association with the risk of pancreatic carcinogenesis: a review. Korean J Gastroenterol 67:168–177
34. Akatsuka S, Toyokuni S (2012) Genome-wide assessment of oxidatively generated DNA damage. Free Radic Res 46:523–530
35. Stolzenberg-Solomon RZ, Graubard BI, Chari S et al (2005) Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. JAMA 294:2872–2878
36. Hirata T, Higashiyama A, Kubota Y et al (2015) HOMA-IR values are associated with glycemic control in Japanese subjects without diabetes or obesity: the KOBE study. J Epidemiol 25:407–414
37. Hanefeld M, Koehler C, Fuecker K, Henkel E, Schaper F, Temelkova-Kurktschiev T (2003) Insulin secretion and insulin sensitivity pattern is different in isolated impaired glucose tolerance and impaired fasting glucose: the risk factor in Impaired glucose tolerance for atherosclerosis and diabetes study. Diabetes Care 26:868–874
38. Abdul-Ghani MA, Williams K, DeFronzo R, Stern M (2006) Risk of progression to type 2 diabetes based on relationship between postload plasma glucose and fasting plasma glucose. Diabetes Care 29:1613–1618
39. Hu FB (2008) Obesity Epidemiology. Oxford University Press, New York
40. Lin Y, Fu R, Grant E et al (2013) Association of body mass index and risk of death from pancreatic cancer in Asians: findings from the Asia Cohort Consortium. Eur J Cancer Prev 22:244–250
41. Lawes CM, Parag V, Bennett DA et al (2004) Blood glucose and risk of cardiovascular disease in the Asia Pacific region. Diabetes Care 27:2836–2842