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ORIGINAL PAPER

Long-term patterns of fasting blood glucose levels and pancreatic cancer incidence

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Abstract

Background Whether type 2 diabetes is cause or consequence, or both, of pancreatic cancer (PaC) remains unresolved. Leveraging repeated measurements of fasting blood glucose (FBG), we examined the temporal relationship between hyperglycemia and PaC incidence.

Methods We conducted a nested case–control study of 278 cases and 826 matched-controls from the Korean National Health Insurance Service-Health Screening Cohort. Over 11 years before index date (date of PaC diagnosis for cases), all participants had at least one FBG measurement in each of the three time windows: −11 to −8, −7 to −4, and −3 to 0 years. Using conditional logistic regression, we estimated odds ratios(ORs) of PaC and 95% confidence intervals (CIs) for hyperglycemia in the overall period and at each interval; for major long-term patterns of FBG across the three intervals (recent-onset, medium-term, and long-standing hyperglycemia).

Results Higher FBG over the past 11 years was associated with an increased odds of PaC ($p_{trend} < .0001$), with recent FBG more predictive of PaC than distant FBG. By FBG assessed in the −3 to 0 interval, OR was 1.97 (95% CI 1.32–2.93) for 110–125 mg/dL and 3.17 (95% CI 2.09–4.80) for ≥126 mg/dL. By long-term patterns of FBG, compared to consistent normoglycemia, OR was 2.02 (95% CI 1.24–3.31) for long-standing hyperglycemia and 3.38 (95% CI 1.87–6.13) for recent-onset hyperglycemia. These associations were more pronounced among never-smokers than ever-smokers ($p_{interaction} = .06$).

Conclusion Recent-onset hyperglycemia may be an early manifestation of undetected PaC, while long-lasting hyperglycemia may serve as a moderate etiologic factor for PaC.

Keywords Hyperglycemia · Fasting blood glucose · Type 2 diabetes · Pancreatic cancer

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Introduction

Pancreatic cancer (PaC), the 12th most commonly diagnosed cancer but the third leading cause of cancer death in the US [1] (and 12th and fifth, respectively, in South Korea) [2], is a relatively rare but highly lethal cancer. After PaC diagnosis, which typically occurs at a late stage, most patients die within a year and only 7.7% survive 5 years [3, 4]. Therefore, prevention and early detection of PaC is of the utmost importance to reduce the burden of PaC. In this regard, type 2 diabetes (T2D) may be particularly relevant, because accumulating evidence suggests that T2D is both a cause and consequence of PaC [5, 6]. From the perspective of T2D being an etiologic factor for PaC, hyperglycemia and hyperinsulinemia associated with T2D have been implicated in pancreatic carcinogenesis. Glucose promotes pancreatic tumor growth [7]. Insulin, through its direct action or by increasing the bioavailability of insulin-like growth factor 1, enhances cell proliferation and inhibits apoptosis [8]. Concerning diabetes being secondary to PaC, the proposed mechanism relates to a paraneoplastic phenomenon by which undetected PaC cells secrete diabetogenic factors to acquire growth advantage [5, 9].

Overall, it has been proposed that long-standing T2D may be a modest risk factor whereas recent-onset diabetes may be an indication of PaC [5, 6]. Yet, previous studies yielded conflicting results on the association between duration of diabetes and PaC incidence [10]. Given that a sizable proportion of diabetes remain undiagnosed in the general population [11], previous studies that relied on self-reported diabetes may have considerably misclassified the duration of T2D. In addition, pathophysiologic processes such as hyperinsulinemia and hyperglycemia occur before the overt diagnosis of T2D. To address the complex temporal relationship of pre-diabetes and diabetes with PaC, a defining characteristic of the optimal study setting is the availability of repeated measurements of fasting blood glucose (FBG) spanning a long period. To date, no epidemiologic study has satisfied this condition. One nested case–control study compared the proportion of individuals with a FBG level of ≥ 126 mg/dL (i.e., FBG cut-off for diabetes) between PaC cases and controls yearly, up to 60 months prior to index date (i.e., date of cancer diagnosis for cases) [12]. Yet, because only a few participants provided multiple FBG measurements, individuals comprising each time interval were different, which limits the comparability of an association between diabetes and FBG across the time intervals. In our study, all participants have at least three FBG measurements collected over a period of 11 years. By leveraging this unique resource, we aimed to comprehensively assess the complex temporal relationship between hyperglycemia and PaC incidence.

Methods

Study population

South Korea implements the mandatory national health insurance program operated by the National Health Insurance Service (NHIS). The NHIS-Health Screening Cohort (NHIS-HEALS) enrolled 514,866 Koreans aged 40 to 70 years in 2002, by randomly sampling 10% of individuals who received a health examination in the 2002–2003 period. As a nationally representative sample, the cohort followed the participants through 2013 years, collecting information on demographics, medical diagnoses and treatments, and results from general health examinations.

We conducted a case–control study nested in this cohort. Cases included all incident PaC (as identified by the International Classification of Diseases, 10th revision, C25) [13] diagnosed between 2010 and 2013 with at least one FBG measurement in each of the three specified intervals (see statistical analysis) and no history of cancer. Eligible controls were cohort participants who were alive without history of cancer at the date of the case's diagnosis (i.e., index date) and have the required FBG data. For each case, we randomly sampled up to four controls from this risk-set, matching age and sex. A total of 278 cases and 826 matched controls were included in the present study. The protocol of this study was approved by the Institutional Review Board (No: 4-2016-1069) at Yonsei University College of Medicine.

Assessment of FBG and other covariates

Under the universal medical coverage in South Korea, all citizens aged 40 years and above can receive a free biennial health examination. Offered at local hospitals following a standard procedure, the check-up includes, among others, a fasting blood test, measurements of height and weight, and self-administered questionnaire on smoking habits, alcohol consumption, and physical activity. Each hospital measured FBG following internal and external quality control procedures directed by the Korean Association of Laboratory Quality Control.

Statistical analysis

To identify timing of FBG most predictive of PaC incidence, from 11 years before index date to index date, we defined three time windows: -11 to -8 years (distant past), -7 to -4 years (mid past), and -3 to 0 years (recent past). When participants had more than one FBG measurement for one interval, an average value was used. Individuals' long-term FBG was estimated by cumulative average from all FBG measurements available. For the overall period and at each

interval, the median FBG among cases and controls was compared using the Wilcoxon rank-sum test.

For FBG, four categories were defined: normoglycemic (< 100 mg/dL), pre-diabetic I (100–109 mg/dL), pre-diabetic II (110–125 mg/dL), and diabetic (≥ 126 mg/dL). Prediabetes was divided into two subtypes, because diagnostic criteria for prediabetes differ between the American Diabetes Association (100–125 mg/dL) and World Health Organization (110–125 mg/dL) [14]. For the overall period and at each interval, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) for the association between FBG and PaC incidence using conditional logistic regression stratified by matching factors (age and sex). The multivariable model was additionally adjusted for established or suspected risk factors of PaC including smoking habits (never, ever), body mass index (BMI <23, 23.0–27.4, ≥ 27.5 kg/m^2), regular physical activity (yes, no), and drinking (yes, no). Test for a linear trend was performed by the Wald test on a score variable created by assigning the median value to each FBG category.

To better understand how timing and duration of hyperglycemia influence PaC incidence, we defined five major FBG trajectories across the three time intervals of − 11 to − 8, − 7 to − 4, and − 3 to 0 years: consistently normoglycemic (< 100, < 100, < 100 mg/dL; reference), recent-onset hyperglycemia (< 100, < 100, ≥ 110 mg/dL), medium-term hyperglycemia (< 100, ≥ 110, ≥ 110 mg/dL), long-standing hyperglycemia (≥ 110, ≥ 110, ≥ 110 mg/dL), and others. These patterns were chosen in light of the trend of increasing FBG with aging. ORs and 95% CIs for the associations between FBG patterns and PaC incidence were calculated using conditional logistic regression. As sensitivity analyses to distinguish the roles of recent-onset hyperglycemia and long-standing hyperglycemia in predicting PaC incidence, we ran a multivariable model simultaneously adjusted for cumulative average of FBGs over the entire period, change in FBGs from the − 11 to − 8 interval to the − 7 to − 4 interval, and that from the − 7 to − 4 interval to the − 3 to 0 interval; a multivariable model including an additional FBG pattern representing normalized or controlled hyperglycemia (≥ 110, ≥ 110 or < 100, < 100 mg/dL).

To examine the robustness of the overall trend of associations between the FBG patterns and PaC incidence and to explore whether the trend varies by major risk factors of PaC, we ran subgroup analyses using unconditional logistic regression adjusted for the matching factors and other relevant covariates. Pre-specified stratifying factors are sex, smoking status, BMI, and physical activity. Tests for interaction were performed by the Wald test on the cross-products term of the FBG pattern (ordinal variable) and stratifying variable (binary variable).

All statistical tests were two-sided, and p values < .05 were considered statistically significant. All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

Characteristics of the source population, as represented by control subjects at index date, are summarized in Table 1. Compared with individuals with normal cumulative average of FBG levels, those in the diabetic range were more likely to be older, male, and ever-smokers and tended to engage in

Table 1 Age-standardized characteristics of controls by cumulative average of fasting blood sugar levels over the past 11 years

	Cumulative fasting blood sugar levels (mg/dL)			
Characteristics[a]	Normal (< 100)	Pre-diabetic I (100–109)	Pre-diabetic II (110–125)	Diabetic (≥ 126)
No of controls	548	150	76	52
Average blood sugar levels (mg/dL)				
Overall period (–11 to 0 years)	90 (5.5)	104 (2.9)	117 (4.8)	156 (30.7)
− 3 to 0 years	93 (9.2)	106 (12.5)	123 (15.5)	147 (25.8)
–7 to − 4 years	90 (9.0)	104 (11.0)	117 (15.2)	150 (30.6)
–11 to − 8 years	88 (10.9)	102 (13.9)	110.0 (15.5)	173 (88.1)
Age at the reference point (years)	56 (9.5)	58 (8.9)	59 (8.5)	61 (8.3)
Women (%)	41	31	30	25
BMI (kg/m^2)	23.8 (2.9)	24.6 (2.5)	25.1 (2.5)	24.7 (1.9)
Ever smokers (%)	50	54	48	61
Regular physical activity (%)	19	27	27	36
Alcohol intake (g/day)	7.5 (15)	10 (16)	11 (15)	8.5 (17)

BMI body mass index

[a]Values are mean (SD) or percentages and all, except age, are standardized to the age distribution of the control at the sampling point

regular physical activity. The higher percentage of physically active individuals with increasing FBG may represent that individuals increase their activity in response to increasing FBG. BMI was higher in pre-diabetes stages than in normoglycemia, but was not further elevated in those with T2D. Although excess adiposity is a dominant risk factor of hyperglycemia [15], BMI does not fully capture visceral adiposity, the metabolically deleterious component, in Asians [16–18].

Over the 11 years before index date, overall FBG was significantly higher among cases than their age- and sex-matched controls (median 98. 6 vs. 94.8 mg/dL; $p = .0002$). The difference was most pronounced during the −3 to 0 interval (median 102.5 vs. 97.4 mg/dL; $p \leq .0001$), less distinct during the −7 to −4 interval, and negligible during the −11 to −8 interval (median 94 vs. 93 mg/dL; $p = .33$) (Fig. 1). Consistent results were observed when median FBG was plotted every 2 years, although not all participants contributed data in each time window (Supplementary Fig. 1). As suggested by Fig. 1, overall FBG was positively associated with the odds of PaC, with the odds significantly elevated even before FBG reached the diagnostic threshold of diabetes (Table 2).

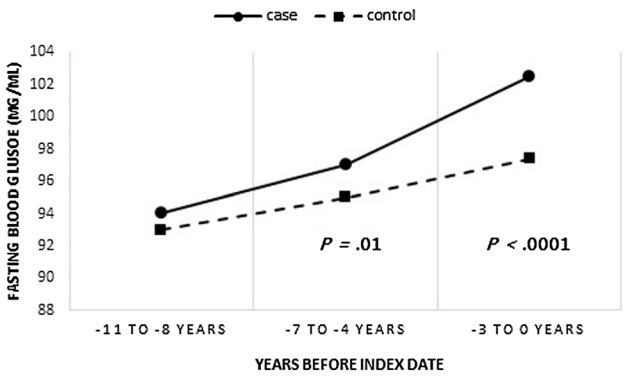

Fig. 1 Median fasting blood glucose of case and control groups across time windows before index date

The multivariable results, which remained virtually unchanged from the results of the base model conditioned on matching factors, showed that the odds of PaC increased 1.90-fold (95% CI 1.22–2.96) in pre-diabetic II individuals and 2.52-fold (95% CI 1.58–4.02) in diabetic individuals (p for trend $\leq .0001$). By time window, recent FBG was more strongly associated with the odds of PaC than distant FBG, with FBG measured further in the past than −7 years no longer predictive of PaC. Notably, in the −3 to 0 interval, the odds of PaC was nearly doubled among the prediabetic II (OR 1.97; 95% CI 1.32–2.93) and more than tripled among the diabetic (OR 3.17; 95% CI 2.09–4.80).

By long-term patterns of FBG reflecting timing and duration of hyperglycemia, compared to consistently normoglycemic individuals, multivariable OR was 2.02 (95% CI, 1.24 to 3.31) for individuals with long-standing hyperglycemia and 3.38 (95% CI 1.87–6.13) for individuals with recent-onset hyperglycemia (Table 3). When long-term FBG, change from the −11 to −8 interval to the −7 to −4 interval, and change from the −7 to −4 interval to the −3

Table 2 ORs and 95% CIs of pancreatic cancer by fasting blood glucose levels at different time windows

Time window of blood glucose measurement	Fasting blood glucose levels (mg/dL)				
	Normal (< 100)	Pre-diabetic I (100–109)	Pre-diabetic II (110–125)	Diabetic (≥ 126)	p_{trend}
Overall period (− 11 to 0 years)					
No. of cases/controls	149/548	54/150	39/76	36/52	
Age and sex stratified	1 (reference)	1.34 (0.93, 1.93)	1.92 (1.24, 2.97)	2.52 (1.59, 4.01)	< .0001
Multivariable[a]	1 (reference)	1.32 (0.91, 1.91)	1.90 (1.22, 2.96)	2.52 (1.58, 4.02)	< .0001
Recent past (− 3 to 0 years)					
No. of cases/controls	119/484	54/166	51/105	54/71	
Age and sex stratified	1 (reference)	1.35 (0.93, 1.95)	1.95 (1.31, 2.90)	3.12 (2.07, 4.70)	< .0001
Multivariable[a]	1 (reference)	1.34 (0.92, 1.95)	1.97 (1.32, 2.93)	3.17 (2.09, 4.80)	< .0001
Mid past (− 7 to − 4 years)					
No. of cases/controls	163/537	46/148	34/79	35/62	
Age and sex stratified	1 (reference)	1.01 (0.69, 1.46)	1.41 (0.91, 2.20)	1.84 (1.16, 2.91)	.01
Multivariable[a]	1 (reference)	0.99 (0.68, 1.44)	1.38 (0.88, 2.16)	1.80 (1.14, 2.86)	.01
Distant past (− 11 to − 8 years)					
No. of cases/controls	187/553	37/135	27/80	27/58	
Age and sex stratified	1 (reference)	0.78 (0.52, 1.18)	1.00 (0.62, 1.60)	1.39 (0.85, 2.28)	.33
Multivariable[a]	1 (reference)	0.77 (0.52, 1.16)	1.00 (0.62, 1.60)	1.36 (0.83, 2.23)	.39

[a]Multivariable analyses were stratified by age (continuous, years) and sex; adjusted for BMI (< 23, 23.0–27.4, ≥ 27.5 kg/m^2), smoking habits (never smoker, ever smoker), regular physical activity (yes, no), drinking (yes, no) at relevant time point

Table 3 ORs and 95% CIs of pancreatic cancer by patterns of fasting blood glucose levels at different time windows

Patterns[a] of fasting blood glucose levels across time intervals (− 11 to − 8, − 7 to − 4, − 3 to 0 years)	No of cases/control[b]	Age and sex stratified	Multivariable[c]
Consistently normoglycemia (N, N, N)	91/329	1 (reference)	1 (reference)
Recent-onset hyperglycemia (N, N, H)	26/28	3.37 (1.86, 6.10)	3.38 (1.87, 6.13)
Medium-term hyperglycemia (N, H, H)	14/17	3.07 (1.46, 6.47)	2.91 (1.37, 6.15)
Long-standing hyperglycemia (H, H, H)	28/55	2.03 (1.25, 3.31)	2.02 (1.24, 3.31)

N normal fasting glucose levels (< 100 mg/dL), *H* high fasting glucose levels (≥ 110 mg/dL)

[a]Patterns of fasting blood glucose levels (consistently normoglycemia, recent-onset hyperglycemia, medium-term hyperglycemia, long-standing hyperglycemia, others) were included in all the models

[b]Numbers of cases and controls do not sum up to total number of cases and controls because not all participants fall into the four patterns of fasting blood glucose levels

[c]Multivariable analyses were stratified by age (continuous, years) and sex; adjusted for BMI (< 23, 23.0–27.4, ≥ 27.5 kg/m^2), smoking status (never smoker, ever smoker), regular physical activity (yes, no), and drinking (yes, no)

to 0 interval were simultaneously adjusted for in a multivariable model, all were independent and significant predictors of PaC incidence, with each 10 mg/dL increase associated with 1.15-fold (95% CI 1.08–1.24), 1.11-fold (95% CI 1.04–1.18), and 1.18-fold (95% CI 1.09–1.27) elevated odds, respectively. No evidence of an elevated PaC incidence was indicated among individuals with normalized or controlled hyperglycemia, although statistical power was limited (Supplementary Table 1). Table 4 shows that recent-onset hyperglycemia remained strongly associated with PaC incidence in most of the subgroups tested, whereas long-standing hyperglycemia did not. The difference between recent-onset and long-standing hyperplasia in predicting PaC incidence was particularly pronounced among never smokers than among ever smokers, with the interaction only marginally insignificant ($p_{\text{interaction}} = .06$).

Table 4 Multivariable[a] ORs and 95% CIs of pancreatic cancer for patterns of fasting blood glucose levels among subgroups

Subgroups	No. of cases/controls	Patterns[b] of fasting blood glucose levels across time intervals (− 11 to − 8, − 7 to − 4, − 3 to 0 years)				$p_{\text{interaction}}$
		Consistently normoglycemia (N-N-N)	Recent-onset hyperglycemia (N-N-H)	Medium-term hyperglycemia (N-H-H)	Long-standing hyperglycemia (H-H-H)	
Sex						
Men	173/520	1 (reference)	3.24 (1.52, 6.92)	2.14 (0.77, 5.95)	1.81 (1.01, 3.26)	0.09
Women	105/306	1 (reference)	3.29 (1.30, 8.32)	3.46 (1.12, 10.66)	0.96 (0.25, 3.66)	
Smoking status						
Never smokers	137/403	1 (reference)	4.90 (2.15, 11.14)	3.50 (1.18,10.33)	1.93 (0.86, 4.30)	0.06
Ever smokers	141/423	1 (reference)	2.27 (0.97, 5.31)	2.15 (0.75, 6.12)	1.53 (0.76, 3.07)	
BMI						
< 23	97/304	1 (reference)	3.43 (1.29, 9.13)	3.96 (0.76, 20.57)	2.79 (1.11, 7.00)	0.33
≥ 23	181/522	1 (reference)	3.24 (1.56, 6.74)	2.48 (1.06, 5.81)	1.49 (0.78, 2.84)	
Physical activity						
Irregular	216/637	1 (reference)	3.00 (1.54, 2.20)	2.71 (1.12, 6.56)	2.32 (1.26, 4.28)	0.93
Regular	62/189	1 (reference)	4.29 (1.25, 14.74)	2.36 (0.56, 10.01)	0.92 (0.32, 2.71)	

N normal fasting glucose levels (< 100 mg/dL), *H* high fasting glucose levels (≥ 110 mg/dL)

[a]From unconditional logistic regression adjusted for age (continuous, years), sex and the same set of covariates at relevant time point as denoted in Table 3 except for the stratifying factor defining the subgroup

[b]Patterns of blood glucose levels (consistently normoglycemia, recent-onset hyperglycemia, medium-term hyperglycemia, long-standing hyperglycemia, others) were included in all the models

Discussion

In this study among Koreans based on at least three FBG levels measured over an 11-year span, we observed a significant positive association between overall FBG and subsequent odds of PaC. A significantly increased odds of PaC already started from the prediabetic II range (FBG 110–125 mg/dL). By timing and duration, PaC incidence was better predicted by FBG in the −3 to 0 interval than in the −7 to −4 interval; by recent-onset hyperglycemia than long-standing hyperglycemia. Regardless, both long-term FBG and recent change in FBG were significantly and independently associated with PaC incidence, which suggests distinct contributions of each measure to the prediction of PaC diagnosis. Further, individuals with hyperglycemia who did not progress to long-term hyperglycemia were not at an elevated odds of PaC. Taken together, our findings provide strong evidence to support that long-standing hyperglycemia may be associated with an increased risk of PaC whereas recent-onset hyperglycemia may be an early manifestation of undetected subclinical PaC.

Several epidemiologic studies have evaluated the association between hyperglycemia and PaC risk. In a recent dose–response meta-analysis of eight prospective studies, a positive linear relationship was identified, with each 10 mg/dL increase in FBG associated with a 14% increased PaC risk across a wide range of FBG (73–189 mg/dL) encompassing normal, prediabetic and diabetic levels [19] Confirming that even prediabetic FBG of 110–125 mg/dL could elevate PaC incidence, we found the timing of FBG relevant to pancreatic carcinogenesis. The progression from normal cells to PaC, to metastatic PaC, and finally to death spans several decades [4]. Based on repeated measurements of FBG obtained from every participant, FBG in the past 7 years was shown to be the strongest predictor of PaC.

In our study, a recent increase in FBG itself predicted PaC incidence above and beyond long-term overall FBG, which reinforces the notion that PaC induces diabetes. At the time of PaC diagnosis, up to two-thirds of patients have diabetes, of which nearly 75% are recent-onset [5]. Furthermore, among PaC patients, recent-onset diabetes often resolves after cancer resection while long-standing diabetes does not [5]. Also considering that most PaC is diagnosed at the end of the natural history of the disease and most patients live for < 12 months [4], recent-onset diabetes reflects events occurring very late in the natural history of PaC.

It is of importance to consider that changes in FBG closely correspond to changes in insulin resistance and insulin secretion in the natural history of T2D. As prediabetes advances to early stages of T2D and then to the late stages, hyperglycemia continues to progress whereas hyperinsulinemia turns into hypoinsulinemia due to decline in pancreatic β-cell function [20]. Thus, increasing duration of hyperglycemia corresponds to decreasing insulin concentrations. A large nested case–control study simultaneously adjusted for pre-diagnostic circulating levels of HbA1C (i.e., a marker of long-term glycemic control), insulin, and proinsulin in a multivariate model, and only proinsulin remained a significant predictor of PaC incidence [21]. Of note, the positive association between proinsulin and PaC incidence was stronger with greater time between blood collection and index date of PaC. If hyperinsulinemia is the causal factor increasing the risk of PaC, the strong association between recent-onset hyperglycemia and PaC observed in our study may reflect peak hyperinsulinemia that occurred years before profound hyperglycemia.

For the strong association between recent-onset hyperglycemia and PaC, an additional or alternative underlying factor may be muscle loss induced by occult PaC. It was shown that whole-body protein breakdown, as indicated by elevated levels of circulating branched-chain amino acids (BCAAs), marks an early consequence of occult PaC [22]. Rapidly proliferating cancer cells, in order to meet their increased needs for amino acids, are hypothesized to induce whole-body protein breakdown [23, 24], and unintended weight loss is a characteristic feature at the time of PaC diagnosis [25]. Of note, circulating BCAAs measured at 2–5 years before diagnosis were particularly strongly predictive of subsequent PaC incidence [22]. In predicting future PaC, this time window of BCAA overlaps with that of FBG in our study. Considering that skeletal muscle is the major site for insulin-mediated glucose uptake [26], reduced muscle mass induced by PaC may contribute to the onset of hyperglycemia. Therefore, recent-onset hyperglycemia, as a correlate of muscle loss induced by subclinical PaC, may be strongly related to PaC incidence.

A distinction between T2D-associated hyperglycemia and PaC-induced hyperglycemia may help better understand clinical implications of our findings for the prevention of PaC. The moderate positive association with long-lasting hyperglycemia may reflect etiologic processes, such as hyperinsulinemia, that increase the risk of PaC. This process may directly influence PaC risk and potentially could be modified through diet, lifestyle, and medications that improve glycemic control. In contrast, recent-onset hyperglycemia that was associated with a notably elevated PaC incidence may be a consequence of disease processes in PaC, and it is unclear if the hyperglycemia is controllable by modifying standard risk factors for T2D, such as obesity [27, 28] and physical inactivity [29, 30]. Indeed, in our subgroup analyses, the association between

recent-onset hyperglycemia and PaC persisted among non-obese and physically active individuals. Whether the hyperglycemia that occurs shortly before diagnosis of PaC, particularly among never smokers, can be utilized for an early detection requires further studies [31].

Our study has important strengths. To our knowledge, this is the first study that used at least three repeated measurements of FBG over an 11-year span to examine the potential bidirectional relationship between FBG and PaC, thereby comprehensively addressing the temporality issue. Additionally, considering that a substantial number of individuals with diabetes in the general population remain undiagnosed [11], our study based on multiple FBG measurements was less prone to misclassification than studies based on self-reported hyperglycemia or diabetes. Its prospective design and sampling of cases and controls from the identical nationally representative database minimize the possibility of recall bias and selection bias, respectively. There are several limitations to our study. Each assessment of FBG is prone to random measurement error and no complementary information such as HbA1c level was available [32]. Thus, we might have underestimated the strength of the true relationship. Due to lack of data on FBG-related factors such as insulin, we could not examine FBG's independent effect and its joint effects with insulin. All of our study participants were Koreans and thus, our findings might not generalize into other ethnic groups. In light of a recent meta-analysis that observed a stronger association between diabetes and PaC incidence in studies from East Asia than in those from Europe and North American [33], our findings are expected to overestimate the risk estimates in other ethnic groups.

In conclusion, recent-onset hyperglycemia, as defined by a sudden increase in FBG level to ≥ 110 mg/dL in the past 3 years, may be a manifestation of PaC, while long-lasting hyperglycemia, as defined by FBG levels consistently ≥ 110 mg/dL in the past 11 years, may serve as a moderate etiologic factor for PaC. While new-onset hyperglycemia may provide a clue to an early detection of PaC, future studies to discover novel biomarkers are warranted to improve the predictability of PaC for its clinical utility. For the prevention of PaC, efforts to reverse prediabetes as well as to treat diabetes should be emphasized.

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Compliance with ethical standards

Conflict of interest The author(s) declare no conflict of interest with NHIS.

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