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Cancer risk according to fasting blood glucose trajectories: a population-based cohort study

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ABSTRACT

Introduction Diabetes mellitus is known to increase the risk of cancer. Fasting blood glucose (FBG) levels can be changed over time. However, the association between FBG trajectory and cancer risk has been insufficiently studied. This research aims to examine the relationship between FBG trajectories and cancer risk in the Korean population.

Research design and methods We analyzed data from the National Health Insurance Service–National Health Screening Cohort collected between 2002 and 2015. Group-based trajectory modeling was performed on 256,271 Koreans aged 40–79 years who had participated in health examinations at least three times from 2002 to 2007. After excluding patients with cancer history before 2008, we constructed a cancer-free cohort. The Cox proportional hazards model was applied to examine the association between FBG trajectories and cancer incidence by cancer type, after adjustments for covariates. Cancer case was defined as a person who was an outpatient thrice or was hospitalized once or more with a cancer diagnosis code within the first year of the claim.

Results During the follow-up time (2008–2015), 18,991 cancer cases were identified. Four glucose trajectories were found: low-stable (mean of FBG at each wave <100 mg/dL), elevated-stable (113–124 mg/dL), elevated-high (104–166 mg/dL), and high-stable (>177 mg/dL). The high-stable group had a higher risk of multiple myeloma, liver cancer and gastrointestinal cancer than the low-stable group, with HR 4.09 (95% CI 1.40 to 11.95), HR 1.68 (95% CI 1.25 to 2.26) and HR 1.27 (95% CI 1.11 to 1.45), respectively. In elevated-stable trajectory, the risk increased for all cancer (HR 1.08, 95% CI 1.02 to 1.16) and stomach cancer (HR 1.24, 95% CI 1.07 to 1.43). Significant associations were also found in the elevated-high group with oral (HR 2.13, 95% CI 1.01 to 4.47), liver (HR 1.50, 95% CI 1.08 to 2.08) and pancreatic cancer (HR 1.99, 95% CI 1.20 to 3.30).

Conclusions Our study highlights that the uncontrolled high glucose level for many years may increase the risk of cancer.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ It is well established that diabetes mellitus (DM) elevates the risk of cancer. However, most published data often required reinterpretation because DM is not a single disease, but a group of metabolic disorders characterized by chronic hyperglycemia.
⇒ Hyperglycemia may appear at the stage of prediabetes. Further studies are needed to investigate the impact of hyperglycemia, including fasting blood glucose (FBG) levels, on cancer incidence and to develop preventive strategies.
⇒ There exists a major research gap because most studies measured FBG levels only at baseline, which may not reflect FBG levels over an extended period and may lead to inaccurate estimations.

WHAT THIS STUDY ADDS

⇒ Our study highlights that the uncontrolled high glucose level for many years may increase the risk of cancer, particularly in the case of digestive cancers.
⇒ FBG trajectories may be a predictive factor for the development of cancer.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further studies are needed to consider longer follow-up times, larger sample sizes, and more frequent FBG measurements to build a more comprehensive understanding of this area.

INTRODUCTION

Diabetes represents an important problem for socioeconomic and public healthcare systems on a global scale, and its burden is anticipated to grow.[1] In South Korea, diabetes is a major contributor to the cause of morbidity and mortality,[2] impacting approximately 6 million Korean adults as of 2021.[3] The association between cancer and diabetes mellitus (DM) has been extensively studied; however, not all studies have yielded consistent findings regarding increased cancer risk in individuals with DM.[4–6] Most published data often required reinterpretation because of the truth that DM is not a single disease, but a group of metabolic disorders characterized by chronic hyperglycemia.[4] There is a long-standing controversy regarding the underlying mechanisms connecting hyperglycemia and cancer.[7–9] In addition, each type of DM has different mechanisms in affected individuals.[10] Furthermore, numerous factors that

contribute to cancer incidence, such as obesity, diet, physical exercise, medication usage, have been identified.[4] Consequently, it is inappropriate to consider patients with DM as a homogeneous group.[4]

As an indication of elevated blood glucose, hyperglycemia may appear at the stage of pre-diabetes or impaired fasting glucose (IFG), in which the level of blood glucose during fasting is higher than the normal stage but does not meet the diagnostic criteria for DM (FBG is between the range of 5.6–6.9 mmol/L and 100–125 mg/dL).[11] This suggests that pre-diabetes or IFG may potentially elevate the risk of cancer development. The age-adjusted prevalence of IFG was 25.0% in 2013 among Korean adults.[2] Additionally, approximately 15.8 million Korean adults are estimated to have pre-diabetes and are at risk of developing DM in 2021,[3] indicating a potential threat posed by hyperglycemia in increasing the risk of cancer. Therefore, further studies are needed to investigate the impact of hyperglycemia, including FBG levels, on cancer incidence and to develop preventive strategies.

Many prospective cohort studies have established a connection between FBG and overall cancer risk,[12] especially gastrointestinal cancer, including stomach,[12 13] colorectal,[14] liver,[15] and pancreas,[16] which can be mediated by chronic hyperglycemia,[17 18] hyperinsulinemia and elevated level of bioavailable IFG.[19] However, FBG levels in individuals may change during follow-up, and most studies measured FBG only at baseline, which may not reflect FBG levels over an extended period and lead to inaccurate estimations. In particular, patients with DM tend to actively manage their blood sugar levels by using glucose-lowering agents or lifestyle modifications, which could introduce bias without accounting for these factors. Considering those limitations, our study will examine FBG trajectories to capture changes in FBG levels over a follow-up period.

Trajectory analysis has recently been applied in epidemiological research to identify similar longitudinal changes over time.[20] Among the different trajectory approaches, group-based trajectory modeling (GBTM) is often selected by researchers owing to its efficiency, fewer errors, and easy of explanation because it is less complex.[21] However, few studies have employed GBTM to track FBG trajectories as well as examine their association with cancer risk based on FBG patterns.[22 23] Given this evidence, it would be meaningful to use GBTM to investigate the link between FBG trajectory and the risk of cancer.

In this research, we conducted a population-based cohort study to investigate FBG trajectories in the Korean population using the GBTM for the purpose of investigating the relationship with several cancer types in both sexes.

METHODS

Data source and study population

Our analysis used data derived from a population-wide cohort at a national level from the National Health Insurance Service–Health Screening Cohort (NHIS-HEALS) database. The NHIS is a single mandatory system covering Korea's entire population and provides a general health screening program to all beneficiaries every 1 or 2 years. The NHIS-HEALs is a cohort of randomly selected 10% of screening participants during 2002–2003 and followed up until 2015.[24] The cohort included 514,866 people aged 40–79 years with essential information, including sociodemographic factors, self-reported health behaviors, clinical laboratory results, and healthcare usage based on insurance claim data.[24]

From the cohort entry 2002–2003, 264,777 subjects who underwent health examinations in three waves, 2002–2003, 2004–2005, and 2006–2007, were included in further analyses. Additionally, 7448 patients were diagnosed with cancer and 539 patients who died before 2008 were excluded to create a cancer-free cohort study. Furthermore, 519 individuals with missing age, sex, and FBG data were excluded. Consequently, our final study cohort comprised 256,271 individuals (figure 1).

Exposure and covariates

Fasting blood glucose

As defined by WHO, FBG levels are measured by taking a blood sample from participants who had fasted for a minimum of 8 hours,[25] measured mmol/L or mg/dL. According to the American Diabetes Association, there are three levels of FBG: normal, pre-diabetes, and diabetes. The pre-diabetes stage includes individuals with FBG concentration of 100–125 mg/dL or 5.6–6.9 mmol/L. Individuals were considered to have diabetes if they had higher FBG levels than the pre-diabetes criterion (FBG level ≥126 mg/dL or 7 mmol/L). On the other hand, they were considered to be in the normal stage (FBG level <100 mg/dL or 5.6 mmol/L).[11]

Covariates

Data on covariates, including sex, age, income level, body mass index (BMI), smoking behaviors, alcohol consumption, exercise, Charlson Comorbidity Index (CCI), family history of DM, presence of DM, use of antidiabetic medications, and presence of chronic viral hepatitis B and C infection, were collected from the first wave in 2002–2003. CCI was treated as continuous variable, while other covariates were considered categorical including age (40–49, 50–59, 60–69, 70–79 years old), income (four quartiles, using income-based insurance premiums as a proxy for income), smoking behaviors (never, former, and current smoker), drinking behaviors (rarely, 2–3 times/month, 1–2 times/week, 3–4 times/week, and almost every day), BMI (underweight: <18.5, normal: 18.5–22.9, overweight: 23–24.9, and obese: ≥25 kg/m^2[26]), exercise (no physical activity, 1–2, 3–4, 5–6 times/week, and every day), presence of DM (yes or no), family history of DM (yes or no), and antidiabetic medications (yes or no). Presence of chronic viral hepatitis B and C infections (yes or no) were adjusted to analyze liver cancer status.

DM diagnosis was determined as meeting one of the two following criteria or both: having a diagnosis code of

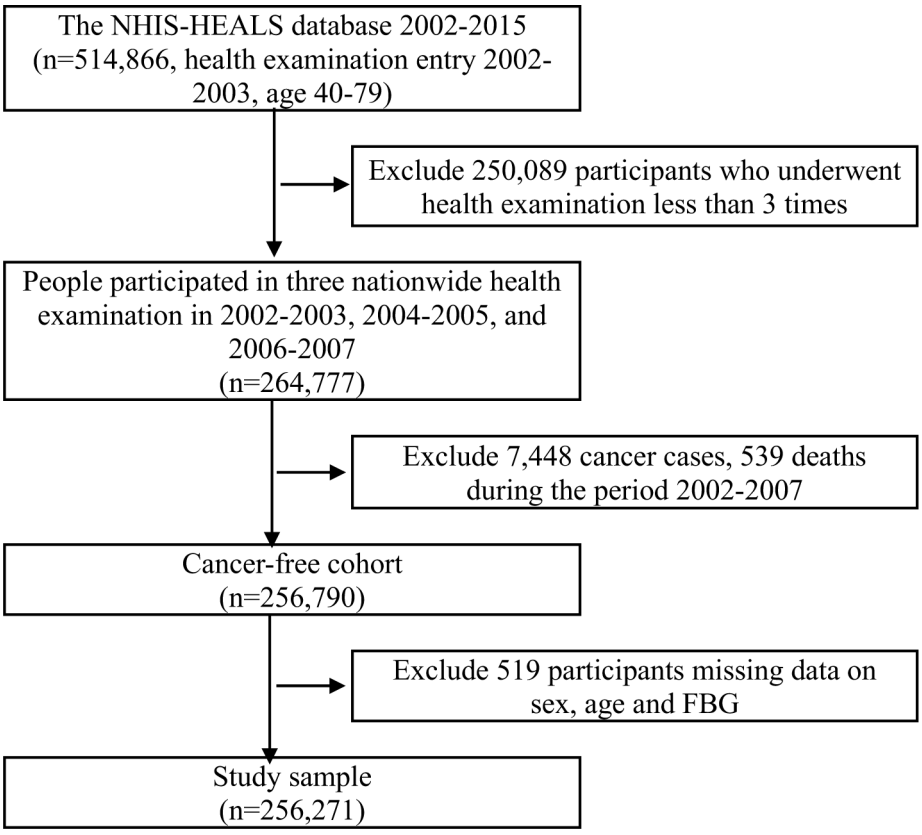

Figure 1 Flowchart of the study population. FBG, fasting blood glucose; NHIS-HEALS, National Health Insurance Service–Health Screening Cohort.

DM (International Classification of Diseases 10th edition (ICD-10) codes), specifically code E10 for type 1 diabetes, E11 to E14 for type 2 diabetes and the prescription of any diabetic agents, or having FBG level ≥126 mg/dL.[27] The use of antidiabetic medication was determined if an individual had at least one claim per year for the relevant prescription.[27]

Case ascertainment

Incident cancers were defined by using primary diagnosis, validated with high sensitivity (>90%) and accuracy (>80% consistency with cancer registry data).[28] An individual who was an inpatient once or outpatient three or more times (ICD code: C00-C97) within the first year of the claim was considered a newly diagnosed patient with cancer. The date of cancer diagnosis was determined as the date on which cancer was first detected.[28] We determined the incidence of 17 specific types of cancer for both sex in the NHIS-HEALS database (according to the GLOBOCAN cancer dictionary), all cancer combined and gastrointestinal cancer (ICD code: C15–C25) including esophagus, stomach, colon, rectum, anus, liver, gallbladder, and pancreatic.

Statistical methods

Group-based trajectory modeling

To calculate changes in FBG, we employed GBTM, a statistical method that determines separate trajectories within a population.[20] To adhere to best practices in latent modeling, which typically require data from multiple time points—at least three occasions, we monitored FBG changes across three waves spanning from 2002 to 2007. The package 'lcmm' in R was used for GBTM analysis.

FBG level was treated as a continuous variable. To determine the best model, we initially checked all the quadratic models from one to six groups, considering that previous studies identified up to five FBG trajectories.[22 23] The optimum number of groups was built on the largest Bayesian Information Criterion (BIC).[20] However, BIC increases when more groups were added to the model. The best-fit model was then identified based on the percentage of group membership (≥1%), model parsimony, as well as distinctiveness (online supplemental table 1). The model with four groups was finally chosen after accessing all the above criteria.

After selecting the number of groups, we determined the polynomial of each group by comparing models with different functional forms based on the significant level (p value <0.05), beginning with the highest polynomial of each group. Finally, the model with four quadratic trajectories was chosen as the best-fitted model (figure 2): 87.78% (N=224,957) of individuals maintained a low FBG concentration (mean FBG at each wave was smaller than 100 mg/dL, referred to as 'low-stable group'); 7.17% (N=18,385) of individuals kept a moderate FBG concentration (mean FBG at each wave ranged from 113 to 124 mg/dL, referred to as 'elevated-stable group');

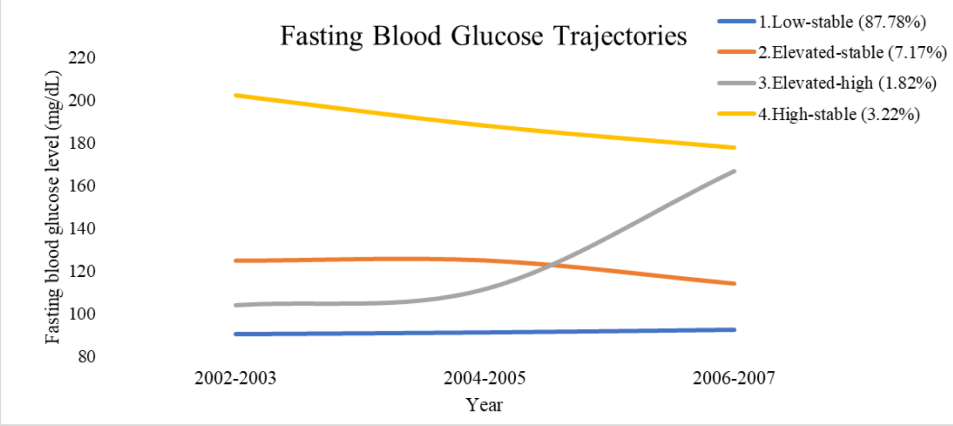

Figure 2 Fasting blood glucose trajectory patterns during 2002–2007.

1.82% (N=4667) of participants initially were at pre-diabetes stage and then progressed to the diabetes stage (mean FBG at each wave ranged from 104 to 166 mg/dL, referred to as 'elevated-high group'); and 3.22% (N=8262) of participants maintained a high FBG concentration (mean FBG at each wave was greater than 177 mg/dL, which is called as 'high-stable group').

Cox proportional hazard models

To compute HRs and 95% CIs for the FBG index relative to the reference group, we used Cox proportional hazard models. The low-stable group served as the reference for comparison with the other trajectories. The censored cases comprised individuals who either died or did not experience an event of interest during the period from 2008 to 2015. The time-to-event (measured in years) was defined as the period starting from January 1, 2008, and ending at either the date of cancer diagnosis date, censoring date, or the end of the following period on December 31, 2015, whichever event came first.

For confounding adjustments, we included the following covariates: sex, age, income level, smoking behaviors, alcohol consumption, BMI, exercise, family history of DM, CCI, DM diagnosis, and antidiabetic medications. The presence of chronic viral hepatitis B and C infections (ICD-10: B18.*) were adjusted to assess liver cancer status.

Cox models were stratified according to types of DM and medication at baseline by including information of DM diagnosis as well as using antidiabetic drugs, and then adjusting for covariates. Analyses of the Cox proportional hazard model were performed using SAS Enterprise Guide V.7.1 (SAS Institute, Cary, North Carolina, USA).

RESULTS

General characteristics of the participants and cancer incidence

The mean age of the 256,271 participants included was 51.27 years (SD=8.87). The mean BMI (kg/m^2) was 23.97 (SD=2.89), and approximately 62.26% of the participants had excess weight (BMI ≥23 kg/m^2). More than half of the participants (52.31%) did not engage in any physical activity. Approximately 62.81% of the participants were non-smokers; around 52.68% reported rarely drinking at the baseline. Nearly 6.26% of participants had a family history of DM (table 1).

Participants in the low-stable group accounted for the highest proportion of the age between 40 and 49 years old. In contrast, a larger percentage of DM, family history of diabetes, and medication users were observed from examinees in the high-stable group than in the other groups (table 1).

By December 31, 2015, 18,991 cancer cases were reported. Stomach cancer (17.20%), colorectal cancer (13.44%), lung cancer (10.82%), and thyroid cancer (12.61%) account for the highest rates of cancers (online supplemental table 2).

Cancer risks according to FBG trajectories

Relative to the low-stable group, HR adjusted for all covariates in the elevated-stable group was 1.08 (95% CI 1.02 to 1.16) for all cancers combined. For each type of cancer, the risk of developing multiple myeloma and malignant plasma cell neoplasms was the strongest in the high-stable group (HR 4.09 (95% CI 1.40 to 11.95)), followed by oral and pancreatic cancer (HR 2.13 (95% CI 1.01 to 4.47) and HR 1.99 (95% CI 1.20 to 3.30), respectively). The risk increased by 50%–68% for liver cancer in elevated-high and high-stable groups. We found significant associations in stomach cancer in elevated-stable (HR 1.24 (95% CI 1.07 to 1.43)) and high-stable group (HR 1.25 (95% CI 1.00 to 1.57)). Significant associations were also observed in gastrointestinal cancer in elevated-stable (HR 1.22 (95% CI 1.12 to 1.34)) and high-stable group (HR 1.27 (95% CI 1.11 to 1.45)) (table 2) (online supplemental table 3).

Regarding the results of subgroup analysis, we divided DM diagnosis into two types: type 1 and type 2. Approximately 85.98% of individuals did not have diagnosis of DM. Most patients with DM had type 2 diabetes, whereas only 2.67% had type 1 diabetes. Of patients with type 1 diabetes, 78.69% were in the low-stable group, indicating

Table 1 General characteristics of study participants by fasting blood glucose trajectory groups at baseline (2002–2003)

	Total (n=256,271)	Low-stable (n=224,957)	Elevated-stable (n=18,385)	Elevated-high (n=4667)	High-stable (n=8262)
Sex (N, %)					
Male	150,832 (58.86)	129,087 (57.38)	12,707 (69.12)	3262 (69.90)	5776 (69.91)
Female	105,439 (41.14)	95,870 (42.62)	5678 (30.88)	1405 (30.10)	2486 (30.09)
Age group (N, %)					
40–49	130,903 (51.08)	119,027 (52.91)	6838 (37.19)	1884 (40.37)	3154 (38.17)
50–59	75,560 (29.48)	64,659 (28.74)	6385 (34.73)	1587 (34.00)	2929 (35.45)
60–69	40,333 (15.74)	33,491 (14.89)	4122 (22.42)	951 (20.38)	1769 (21.41)
70–79	9475 (3.70)	7780 (3.46)	1040 (5.66)	245 (5.25)	410 (4.96)
Income (N, %)					
Q1 (lowest)	37,503 (14.63)	32,535 (14.46)	2827 (15.38)	795 (17.03)	1346 (16.29)
Q2	51,851 (20.23)	45,107 (20.05)	3925 (21.35)	1082 (23.18)	1737 (21.02)
Q3	72,821 (28.42)	63,689 (28.31)	5379 (29.26)	1374 (29.44)	2379 (28.79)
Q4 (highest)	94,096 (36.72)	83,626 (37.17)	6254 (34.02)	1416 (30.34)	2800 (33.89)
Smoking status (N, %)					
Missing	10,976 (4.28)	9611 (4.27)	787 (4.28)	224 (4.80)	354 (4.28)
Never smoker	160,954 (62.81)	143,355 (63.73)	10,488 (57.05)	2543 (54.49)	4568 (55.29)
Former smoker	24,284 (9.48)	20,989 (9.33)	2071 (11.26)	450 (9.64)	774 (9.37)
Current smoker	60,057 (23.43)	51,002 (22.67)	5039 (27.41)	1450 (31.07)	2566 (31.06)
Alcohol consumption (N, %)					
Missing	4663 (1.82)	4055 (1.80)	356 (1.94)	94 (2.01)	158 (1.91)
Rarely drinking	135,012 (52.68)	120,176 (53.42)	8610 (46.83)	2222 (47.61)	4004 (48.46)
2–3 times/month	42,877 (16.73)	38,039 (16.91)	2898 (15.76)	740 (15.86)	1200 (14.52)
1–2 times/week	46,376 (18.10)	39,992 (17.78)	3783 (20.58)	935 (20.03)	1666 (20.16)
3–4 times/week	17,753 (6.93)	14,826 (6.59)	1724 (9.38)	424 (9.09)	779 (9.43)
Almost everyday	9590 (3.74)	7869 (3.50)	1014 (5.52)	252 (5.40)	455 (5.51)
Physical activity (N, %)					
Missing	7036 (2.75)	6231 (2.77)	467 (2.54)	137 (2.94)	201 (2.43)
None	134,057 (52.31)	118,263 (52.57)	9347 (50.84)	2373 (50.85)	4074 (49.31)
1–2 times/week	65,816 (25.68)	57,653 (25.63)	4710 (25.62)	1217 (26.08)	2236 (27.06)
3–4 times/week	26,068 (10.17)	22,946 (10.20)	1874 (10.19)	442 (9.47)	806 (9.76)
5–6 times/week	7023 (2.74)	6115 (2.72)	537 (2.92)	143 (3.06)	228 (2.76)
Almost everyday	16,271 (6.35)	13,749 (6.11)	1450 (7.89)	355 (7.61)	717 (8.68)
Body mass index (N, %)					
Underweight	5735 (2.24)	5299 (2.36)	257 (1.40)	75 (1.61)	104 (1.26)
Normal weight	90,959 (35.49)	83,010 (36.90)	4667 (25.38)	1091 (23.38)	2191 (26.52)
Overweight	71,947 (28.07)	63,405 (28.19)	5042 (27.42)	1232 (26.40)	2268 (27.45)
Obese	87,630 (34.19)	73,243 (32.56)	8419 (45.79)	2269 (48.62)	3699 (44.77)
Charlson Comorbidity Index (N, %)					
0	144,136 (56.24)	130,159 (57.86)	8638 (46.98)	2217 (47.50)	3122 (37.79)
≥1	112,135 (43.76)	94,798 (42.14)	9747 (53.02)	2450 (52.50)	5140 (62.21)
Diabetes mellitus diagnosis (N, %)					
No	233,413 (91.08)	220,336 (97.95)	9102 (49.51)	3188 (68.31)	787 (9.53)
Yes	22,860 (8.92)	4621 (2.05)	9283 (50.49)	1479 (31.69)	7475 (90.47)
Antidiabetic medication (N, %)					
No	244,558 (95.43)	222,669 (98.98)	14,672 (79.8)	3546 (75.98)	3671 (44.43)
Yes	11,713 (4.57)	2288 (1.02)	3713 (20.20)	1121 (24.02)	4591 (55.57)

Continued

Table 1 Continued

	Total (n=256,271)	Low-stable (n=224,957)	Elevated-stable (n=18,385)	Elevated-high (n=4667)	High-stable (n=8262)
Family history of diabetes (N, %)					
Missing	29,278 (11.42)	25,824 (11.48)	2094 (11.39)	486 (10.41)	874 (10.58)
No	210,940 (82.31)	186,540 (82.92)	14,546 (79.12)	3696 (79.19)	6158 (74.53)
Yes	16,053 (6.26)	12,593 (5.60)	1745 (9.49)	485 (10.39)	1230 (14.89)

that these patients adhered to use medications and were able to control their FBG level. In contrast, approximately 18.61% of patients with type 2 diabetes maintain normal FBG levels. A significant association was observed in patients without DM in the elevated-stable group (HR 1.09 (95% CI 1.01 to 1.18)). There was no significant difference in cancer risk in the other trajectory groups and in the DM group (online supplemental table 4).

Table 2 Adjusted HRs (95% CI) for the association between FBG trajectories and the cancer risk

	Fasting blood glucose trajectories				
Cancer types	**Groups**	**Case**	**aHR (95% CI)***	**aHR (95% CI)†**	**aHR (95% CI)‡**
All cancer types	Low-stable	16,140	Reference	Reference	Reference
	Elevated-stable	1717	1.11 (1.06 to 1.17)	1.10 (1.04 to 1.15)	1.08 (1.02 to 1.16)
	Elevated-high	378	1.01 (0.91 to 1.11)	1.01 (0.91 to 1.12)	0.98 (0.87 to 1.10)
	High-stable	756	1.14 (1.06 to 1.22)	1.11 (1.03 to 1.20)	1.07 (0.97 to 1.19)
Gastrointestinal cancer	Low-stable	6895	Reference	Reference	Reference
	Elevated-stable	904	1.29 (1.20 to 1.38)	1.26 (1.18 to 1.36)	1.22 (1.12 to 1.34)
	Elevated-high	192	1.13 (0.98 to 1.30)	1.12 (0.97 to 1.30)	1.08 (0.92 to 1.27)
	High-stable	437	1.44 (1.31 to 1.59)	1.42 (1.28 to 1.56)	1.27 (1.11 to 1.45)
Oral cancer	Low-stable	175	Reference	Reference	Reference
	Elevated-stable	21	1.22 (0.77 to 1.92)	1.18 (0.74 to 1.88)	0.95 (0.52 to 1.76)
	Elevated-high	9	2.13 (1.09 to 4.16)	2.15 (1.10 to 4.22)	2.13 (1.01 to 4.47)
	High-stable	10	1.33 (0.70 to 2.52)	1.33 (0.70 to 2.52)	1.11 (0.47 to 2.65)
Stomach cancer	Low-stable	2706	Reference	Reference	Reference
	Elevated-stable	344	1.25 (1.12 to 1.40)	1.20 (1.07 to 1.35)	1.24 (1.07 to 1.43)
	Elevated-high	60	0.90 (0.70 to 1.16)	0.93 (0.72 to 1.20)	0.90 (0.68 to 1.19)
	High-stable	156	1.31 (1.12 to 1.54)	1.30 (1.10 to 1.53)	1.25 (1.00 to 1.57)
Liver cancer	Low-stable	1103	Reference	Reference	Reference
	Elevated-stable	164	1.46 (1.24 to 1.72)	1.48 (1.25 to 1.75)	1.22 (0.98 to 1.51)
	Elevated-high	45	1.63 (1.21 to 2.20)	1.66 (1.23 to 2.25)	1.50 (1.08 to 2.08)
	High-stable	107	2.19 (1.80 to 2.67)	2.11 (1.72 to 2.59)	1.68 (1.25 to 2.26)
Pancreatic cancer	Low-stable	407	Reference	Reference	Reference
	Elevated-stable	54	1.28 (0.96 to 1.71)	1.24 (0.93 to 1.67)	1.32 (0.92 to 1.91)
	Elevated-high	19	1.89 (1.19 to 2.99)	1.99 (1.25 to 3.15)	1.99 (1.20 to 3.30)
	High-stable	31	1.74 (1.20 to 2.50)	1.75 (1.20 to 2.54)	1.64 (0.97 to 2.78)
Multiple myeloma and malignant plasma cell neoplasms	Low-stable	111	Reference	Reference	Reference
	Elevated-stable	11	0.97 (0.52 to 1.81)	0.98 (0.53 to 1.84)	1.19 (0.54 to 2.61)
	Elevated-high	3	1.10 (0.35 to 3.45)	0.75 (0.19 to 3.04)	0.53 (0.07 to 3.85)
	High-stable	8	1.63 (0.79 to 3.34)	1.67 (0.81 to 3.42)	4.09 (1.40 to 11.95)

*Adjusted for age, sex.
†Adjusted for age, sex, smoking behaviors, alcohol consumption.
‡Adjusted for age, sex, income level, smoking behaviors, alcohol consumption, body mass index, physical activity, family history of diabetes, Charlson Comorbidity Index, diabetes mellitus diagnosis, and antidiabetic medications.
aHRs, adjusted HRs.

Glucose-lowering agents were divided into seven subgroups existing in 2002–2003 NHIS-HEALS data: insulin, sulfonylureas, metformin, meglitinide, thiazolidinedione, acarbose, and combined therapy which included two or more classes of antidiabetic agents. Sulfonylureas and metformin were the most commonly used drugs for treatment (>87%). No significant association was observed among medication users except for participants taking medications from acarbose in the elevated-high group. In this group, the risk of developing cancer was approximately 2.5-fold higher than that of the reference group (HR 2.54 (95% CI 1.04 to 6.19)) (online supplemental table 5).

DISCUSSION

We applied trajectory analysis to examine changes in FBG levels at three different time points between 2002 and 2007, which enabled us to identify four distinct trajectory groups. The most prevalent group was the low-stable group, which constituted 87.78% of the sample population. The elevated-stable, high-stable, and elevated-high groups accounted for 7.17%, 3.22%, and 1.82% of the population, respectively. Notably, previous research exploring FBG trajectories reported varying numbers of trajectories, typically ranging from four to five.[22 23 29] Similarly, a prior study conducted in Korea by Jeon *et al* also investigated FBG trajectories and identified four distinct patterns.[23] However, the distribution and proportion of each trajectory group in our study differed from those observed in the aforementioned study. Specifically, four groups included low-stable, moderate-stable, elevated-upward, and high-upward with the percentage of each group were 47.9%, 44.1%, 6.7%, and 14.0%, respectively.[23] This difference is due to dissimilarities in the targeted population, sample size, and follow-up duration. Notably, our study used a larger sample size and included participants aged between 40 and 79 years who were at high risk, whereas the study of Jeon *et al* recruited examinees starting from 20 years of age.[23]

Our analysis identified positive relations between FBG trajectories and the risks of overall cancers, gastrointestinal cancer, as well as several specific cancers (multiple myeloma and malignant plasma cell neoplasms, oral, stomach, liver, and pancreatic cancer). A previous study in China also explored FBG trajectories and their association with overall cancers and digestive cancers.[22] Significant associations with all cancers and digestive cancers were observed in low-stable and elevated-stable groups.[22] However, because of the limited number of cancer cases, a detailed analysis of site-specific cancers could not be extensively conducted.[22]

An elevated risk for overall cancers was observed in the elevated-stable group, which provides a potential suggestion for further investigations into the prediabetic population in the future. While past research consistently indicates a positive association between a history of diabetes and cancer risk, suggesting that the high-stable group may be closely linked to an elevated risk of total cancer, our study produced conflicting results.[4 5] This discrepancy may be attributed to the predominance of diabetic individuals in this group, comprising over 90% of the sample. While both adjusted HR for all cancer combined in model 1 and model 2 in table 2 showed significant results, this became non-significant after adjusting for diabetes diagnosis. Regarding increase cancer risk in patients with elevated FBG, a prospective cohort study found a significant association between FBG levels ranging from 110 to 125 mg/dL and cancer risk in males, but not in females.[30] Other studies have also documented an elevated risk of cancer in prediabetic individuals, accompanied by higher mortality from certain types of cancer.[12 19 31] Several biological mechanisms underlie this association. Hyperglycemia-induced accumulation of advanced glycation end-products and the generation of oxidative stress may promote cancer development.[32] Furthermore, hyperinsulinemia and increased level of bioavailable IGF, which are associated with insulin resistance,[33] may contribute to cancer cell proliferation.[34]

Few studies may evaluate the association with specific cancers such as multiple myeloma and malignant plasma cell neoplasms because of insufficient numbers of cancer cases. In this study, we observed a strong positive association with high-stable group for these specific cancers; however, the estimations were based on the small number of cases. To our knowledge, positive associations between FBG and oral cancer have not been described previously, which is required for further investigation.

Gastrointestinal cancers, including pancreatic, stomach, and liver cancer, are widely acknowledged to be closely linked to elevated FBG levels.[13 15 16] In line with previous research, our study revealed significant findings in these specific cancer types, although the patterns varied among different groups. The potential results may be contributed by the high number of patients with diabetes in high-stable group. Furthermore, some individuals may have diabetes but may not have sought medical attention, leading to an underdiagnosis despite displaying elevated FBG level in those patients. These may affect to the estimation in final model after adjusting for diabetes diagnosis covariate.

Our subgroup analysis revealed a high overall cancer risk in the elevated-stable group among subjects without a diagnosis of DM. The risk increased in individuals with elevated FBG levels but did not meet the diagnostic criteria for DM, according to the current American Diabetes Association definition of pre-diabetes.[11] It suggests that individuals with persistently uncontrolled high glucose levels over an extended period may have an increased risk of cancer. This finding has important public health implications because, in the Korean population, the prevalence of pre-diabetes tended to increase over time from 21.5% in 2006 to 25.0% in 2013.[2] Considering the substantial prevalence of pre-diabetes and its association with cancer risk, implementing interventions

targeting this large population could have a major impact on public health.

The cancer risk among the diabetic population may be influenced by certain therapies used for diabetic treatment, potentially through their impact on insulin levels.[35] In the case of acarbose, treatment did not show significant differences in cancer incidence in previous studies.[35] Contrastingly, we did not find a significant association between cancer risk and most types of therapy, except for that with acarbose. We observed that patients with DM in the elevated-high group had a greater risk of cancer than those in the low-stability group, even when using acarbose to manage their blood sugar levels. Acarbose blocks the breakdown of starches in the intestine, thereby slowing the rise in blood glucose levels after a meal.[11] However, acarbose is not a primary choice in clinical practice, following the guidelines for using glucose-lowering medication use,[36] which may explain the limited number of cases using acarbose in our research. Thus, our evaluation was limited and lacked sufficient statistical power, resulting in divergent findings compared with the findings of previous research.

In our analysis, cancer risk did not increase when treating metformin in all FBG patterns. Numerous studies have suggested that metformin plays a protective role in cancer development. A nested case-control study involving female users of oral antidiabetic drugs conducted in the UK reported that prolonged use of metformin linked with a reduced risk of developing breast cancer, compared with non-use of metformin.[37] Additionally, each gram added to the metformin dose has been associated with a 42% decline in cancer mortality.[37] The mechanism is far from clear, but it has been observed that adenosine monophosphate-activated protein kinase (AMPK)—activated by metformin— leads to a strong suppression of cell proliferation in malignant as well as non-malignant cells.[38] This effect may be mediated through cell-cycle regulation and inhibition of protein synthesis.[38]

Our study had several notable strengths. First, we used data from the NHIS-HEALS, which covered a large sample size and a long follow-up duration (7.6 years). Second, we employed trajectory analysis, specifically the GBTM, to identify the FBG patterns. Moreover, this study was based on measuring FBG, rather than self-reported information, which helped to mitigate recall bias or misclassification. Furthermore, our study stands out as one of the few to incorporate medication use as a covariate in the analysis.

However, this study had some limitations. The first was the relatively short timeframe over which FBG changes were measured (6 years—three waves). Although no existing publications have captured lifelong FBG measurements, this limitation should be acknowledged. It is important to note that certain cancer types, such as breast, prostate, or testicular cancer, were not available in the NHIS-HEALS dataset owing confidentiality, thus limiting our analysis in these specific cancer categories. However, this is one of the few studies to assess cancer risk related to FBG trajectories. Third, associations with DM diagnosis as well as antidiabetic medications may not have been fully evaluated, as the limited number of cases after subgroup analysis could not provide enough statistical power. Fourth, although some important covariates were adjusted, residual confounders may exist, for example, family history of cancer. Fifth, our dataset lacked certain tests that reflect long-term glucose metabolism, such as HbA1c or oral glucose tolerance tests, which may result in misclassifications within the pre-diabetes and diabetes groups. Lastly, our cohort study's population may not fully represent the entire Korean population because it included participants aged greater than 40 who underwent multiple check-ups between 2002 and 2007. Thus, the characteristics of patients who participated in screening programs may differ from those of patients who did not participate.

In conclusion, our analysis will contribute to the understanding of the link between cancer risk and changes in FBG levels. Our findings revealed relationships between FBG patterns and the risk of overall cancer, especially gastrointestinal cancer, and several specific types of cancer such as multiple myeloma and malignant plasma cell neoplasms, oral, liver, stomach, and pancreatic cancer. These results suggested that individuals in the pre-diabetes stage may be at an increased risk of developing cancer. Future studies should consider longer follow-up times, larger sample sizes, and more frequent FBG measurements to gain a more comprehensive understanding of this area.

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Data availability statement Data are available upon reasonable request. The HEALS dataset is available on request from the National Health Insurance Sharing Service, https://nhiss.nhis.or.kr/.

Author note This study was designed and conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

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Supplement Table 1: Trajectory model selection

Number of groups	Selected (Yes/No)	Selection criteria for the group number			
		BIC	Parsimony	Group membership ≥ 1% in all groups	Distinctive features
1	No		+	+	
2	No		+	+	
3	No		+	+	+
4	Yes	+		+	++
5	No	+		+	++
6	No	+		Cannot convergence	Cannot convergence

Supplement Table 2: Number of cancer incidences during 2008-2015

Cancer types	**ICD-10**	**N (%)**
Lip, oral cavity, and pharynx	C00-14	215(1.13)
Esophagus	C15	199(1.05)
Stomach	C16	3266(17.20)
Colon and rectum	C18-20	2548(13.44)
Liver	C22	1419(7.48)
Gallbladder and biliary tract	C23-24	483(2.54)
Pancreas	C25	511(2.69)
Larynx	C32	151(0.80)
Lung	C33-34	2055(10.82)
Kidney	C64	356(1.87)
Bladder	C67	529(2.78)
Brain	C70-72	189(1.00)
Thyroid gland	C73	2397(12.61)
Hodgkin lymphoma	C81	12(0.06)
Non-Hodgkin lymphoma	C82-86,96	360(1.90)
Multiple myeloma, malignant plasma cell neoplasms	C90	133(0.70)
Leukemia	C91-95	183(0.96)
Others	Others	3985(20.99)
Total	**C00-97**	**18991**

ICD-10, the International Classification of Diseases 10th Revision

Supplement Table 3: Adjusted hazard ratios[a] (95% confidence interval) for the association between FBG trajectories and the cancer risk.

Cancer types	Fasting blood glucose trajectories				
	Groups	**Case**	**aHR (95% CI)[1]**	**aHR (95% CI)[2]**	**aHR (95% CI)[3]**
Esophagus cancer	Low-stable	165	Reference	Reference	Reference
	Elevated-stable	22	1.17 (0.75,1.82)	1.12 (0.71,1.76)	1.60 (0.94,2.73)
	Elevated-high	3	0.67 (0.21,2.09)	0.23 (0.03,1.62)	0.29 (0.04,2.10)
	High-stable	9	1.12 (0.57,2.19)	1.12 (0.57,2.19)	1.49 (0.59,3.80)
Colorectal cancer	Low-stable	2115	Reference	Reference	Reference
	Elevated-stable	264	1.24 (1.09,1.41)	1.25 (1.10,1.42)	1.17 (0.99,1.38)
	Elevated-high	52	1.00 (0.76,1.32)	0.97 (0.73,1.30)	0.88 (0.64,1.21)
	High-stable	117	1.27 (1.05,1.53)	1.24 (1.03,1.51)	1.06 (0.81,1.38)
Gallbladder & biliary tract cancer	Low-stable	397	Reference	Reference	Reference
	Elevated-stable	56	1.35 (1.02,1.79)	1.26 (0.94,1.68)	1.2 (0.82,1.76)
	Elevated-high	13	1.32 (0.76,2.30)	1.25 (0.71,2.23)	1.47 (0.83,2.61)
	High-stable	17	0.97 (0.60,1.58)	0.99 (0.61,1.61)	0.72 (0.36,1.45)
Larynx cancer	Low-stable	126	Reference	Reference	Reference
	Elevated-stable	11	0.76 (0.41,1.42)	0.80 (0.43,1.47)	0.71 (0.32,1.57)
	Elevated-high	5	1.44 (0.59,3.52)	1.49 (0.61,3.65)	1.28 (0.45,3.63)
	High-stable	9	1.45 (0.74,2.85)	1.47 (0.75,2.89)	1.34 (0.51,3.50)
Lung cancer	Low-stable	1740	Reference	Reference	Reference
	Elevated-stable	192	1.00 (0.86,1.16)	1.00 (0.86,1.17)	0.96 (0.79,1.17)
	Elevated-high	40	0.88 (0.64,1.20)	0.86 (0.62,1.18)	0.86 (0.61,1.22)
	High-stable	83	1.03 (0.82,1.28)	1.01 (0.80,1.26)	0.94 (0.70,1.27)
Kidney cancer	Low-stable	305	Reference	Reference	Reference
	Elevated-stable	36	1.26 (0.89,1.78)	1.27 (0.89,1.80)	1.15 (0.73,1.81)
	Elevated-high	6	0.84 (0.37,1.89)	0.88 (0.39,1.98)	0.45 (0.14,1.44)
	High-stable	9	0.72 (0.37,1.39)	0.74 (0.38,1.44)	0.68 (0.29,1.58)

Bladder cancer	Low-stable	455	Reference	Reference	Reference
	Elevated-stable	44	0.86 (0.63,1.18)	0.80 (0.58,1.12)	0.90 (0.61,1.35)
	Elevated-high	10	0.82 (0.44,1.54)	0.87 (0.47,1.63)	0.64 (0.29,1.46)
	High-stable	20	0.93 (0.59,1.45)	0.92 (0.58,1.45)	1.33 (0.72,2.46)
Brain cancer	Low-stable	165	Reference	Reference	Reference
	Elevated-stable	16	1.01 (0.60,1.69)	1.06 (0.63,1.78)	1.34 (0.72,2.49)
	Elevated-high	5	1.29 (0.53,3.15)	1.38 (0.57,3.36)	1.65 (0.66,4.14)
	High-stable	3	0.44 (0.14,1.37)	0.47 (0.15,1.46)	0.44 (0.09,2.02)
Thyroid cancer	Low-stable	2204	Reference	Reference	Reference
	Elevated-stable	130	1.03 (0.86,1.23)	1.03 (0.86,1.24)	1.02 (0.81,1.29)
	Elevated-high	21	0.65 (0.42,0.99)	0.62 (0.39,0.97)	0.64 (0.40,1.03)
	High-stable	42	0.74 (0.55,1.01)	0.69 (0.50,0.96)	0.74 (0.50,1.11)
Hodgkin lymphoma	Low-stable	9	Reference	Reference	Reference
	Elevated-stable	2	2.36 (0.50,11.08)	2.35 (0.49,11.17)	2.88 (0.47,17.66)
	Elevated-high	0	n/a	n/a	n/a
	High-stable	1	2.72 (0.34,21.63)	2.65 (0.33,21.3)	2.05 (0.12,36.70)
Non-Hodgkin lymphoma	Low-stable	311	Reference	Reference	Reference
	Elevated-stable	26	0.90 (0.60,1.34)	0.94 (0.63,1.41)	0.81 (0.48,1.37)
	Elevated-high	9	1.26 (0.65,2.45)	1.33 (0.69,2.58)	1.37 (0.66,2.83)
	High-stable	14	1.11 (0.65,1.90)	1.08 (0.62,1.88)	0.93 (0.43,1.99)
Leukemia	Low-stable	157	Reference	Reference	Reference
	Elevated-stable	20	1.33(0.83,2.12)	1.32 (0.82,2.14)	1.38 (0.74,2.57)
	Elevated-high	4	1.09(0.40,2.93)	1.14 (0.42,3.08)	0.99 (0.31,3.19)
	High-stable	2	0.31(0.08,1.24)	0.16 (0.02,1.14)	0.19 (0.02,1.55)

aHR, adjusted hazard ratios.

CI, confidence interval.

[1] Adjusted for age, sex.

[2] Adjusted for age, sex, smoking behaviors, alcohol consumption.

[3]Adjusted for age, sex, income level, smoking behaviors, alcohol consumption, body mass index, physical activity, family history of diabetes, Charlson comorbidity index, diabetes mellitus diagnosis, and antidiabetic medications.

Supplementary Table 4: Adjusted hazard ratios[a] (95% confidence interval) for the association between fasting blood glucose trajectories and the cancer risk by diabetes diagnosis subgroup.

Diabetes diagnosis	Fasting blood glucose trajectories		
	Groups	**Cases**	**aHR (95% CI)**
No diabetes mellitus	Low-stable	220336	Reference
	Elevated-stable	9102	1.09 (1.01,1.18)
	Elevated-high	3188	0.99 (0.86,1.14)
	High-stable	787	0.92 (0.69,1.22)
Diabetes mellitus type I	Low-stable	480	Reference
	Elevated-stable	77	0.64 (0.22,1.85)
	Elevated-high	34	0.90 (0.26,3.18)
	High-stable	19	0.42 (0.05,3.27)
Diabetes mellitus type II	Low-stable	4141	Reference
	Elevated-stable	9206	1.09 (0.96,1.25)
	Elevated-high	1445	0.96 (0.77,1.20)
	High-stable	7456	1.09 (0.95,1.25)

aHR, adjusted hazard ratios.

CI, confidence interval.

[a]Adjusted for age, sex, income level, smoking behaviors, alcohol consumption, body mass index, physical activity, family history of diabetes, Charlson comorbidity index, and antidiabetic medications.

Supplementary Table 5: Adjusted hazard ratios[a] (95% confidence interval) for the association between fasting blood glucose trajectories and the cancer risk by medications subgroup.

Medication	Fasting blood glucose trajectories		
	Groups	**Cases**	**aHR (95% CI)**
Insulin	Low-stable	28	Reference
	Elevated-stable	41	1.49 (0.24,9.11)
	Elevated-high	18	0.86 (0.1,7.74)
	High-stable	96	0.43 (0.06,2.98)
Sulfonylureas	Low-stable	1610	Reference
	Elevated-stable	2542	1.12 (0.91,1.4)
	Elevated-high	753	0.97 (0.72,1.32)
	High-stable	3012	1.08 (0.87,1.35)
Metformin	Low-stable	552	Reference
	Elevated-stable	858	1.33 (0.9,1.96)
	Elevated-high	246	1.33 (0.79,2.23)
	High-stable	1094	1.13 (0.77,1.67)
Meglitinide	Low-stable	14	Reference
	Elevated-stable	22	n/a
	Elevated-high	8	n/a
	High-stable	23	n/a
Thiazolidinedione	Low-stable	48	Reference
	Elevated-stable	74	1.99 (0.29,13.88)
	Elevated-high	21	1.58 (0.08,29.87)
	High-stable	111	2.86 (0.38,21.41)
Acarbose	Low-stable	24	Reference
	Elevated-stable	43	1.47 (0.69,3.12)
	Elevated-high	18	2.54 (1.04,6.19)
	High-stable	48	1.82 (0.88,3.75)
Combined therapy	Low-stable	188	Reference
	Elevated-stable	273	0.54 (0.05,5.37)
	Elevated-high	91	n/a
	High-stable	357	0.21 (0.02,2.36)

aHR, adjusted hazard ratios.

CI, confidence interval.

[a]Adjusted for age, sex, income level, smoking behaviors, alcohol consumption, body mass index, physical activity, family history of diabetes, Charlson comorbidity index, and diabetes mellitus diagnosis.