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ORIGINAL ARTICLE

Diabetes mellitus is associated with an increased risk of gastric cancer: a cohort study

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Abstract

Background Diabetes mellitus (DM) has been considered a potential risk factor for gastric cancer, but the evidence is conflicting. We evaluated the association of DM with incident gastric cancer in a large cohort of men and women with endoscopic assessment at baseline and during follow-up.

Methods We performed a retrospective cohort study of 195,312 adult men and women who underwent upper endoscopy at baseline and during follow-up between 2003 and 2014. DM was defined as fasting serum glucose ≥ 126 mg/dL, self-reported history of DM or current use of antidiabetic medications. Gastric cancer was confirmed histologically.

Results The prevalence of DM at baseline was 3.0% ($n = 5774$). Over 865,511 person-years of follow-up, 198 participants developed gastric cancer. The fully adjusted hazard ratio (HR) for incident gastric cancer comparing participants with and without DM at baseline was 1.76 [95% confidence interval (CI) 1.04–2.97; $P = 0.033$). When we evaluated DM as a time-varying covariate, the fully adjusted HR was 1.66 (95% CI 1.04–2.68; $P = 0.036$). The association between DM and incident gastric cancer did not differ by the presence of intestinal metaplasia (P for interaction = 0.61).

Conclusions In this large cohort with endoscopic follow-up, DM was independently associated with increased gastric cancer incidence. The increased risk was independent of mucosal atrophy and intestinal metaplasia and was consistent in participants with newly developed DM during follow-up. Patients with DM may require more intensive endoscopic follow-up for gastric cancer screening.

Keywords Cohort studies · Diabetes mellitus · Gastric cancer · Gastroscopy · Stomach neoplasms

Introduction

Gastric cancer is the fifth most common cancer and the third most common cause of cancer mortality worldwide [1]. Despite its decreasing incidence and mortality, gastric cancer was responsible for 1,033,701 new cases and 782,685 deaths globally in 2018 [1]. *Helicobacter pylori* infection is a well-known cause of gastric cancer [2, 3]. *H. pylori* induced chronic inflammation may lead to gastric mucosal atrophy and intestinal metaplasia that eventually results in the development of gastric cancer [4]. Other risk factors for gastric cancer include age, sex, smoking, and alcohol consumption [5–8].

Diabetes mellitus (DM), a metabolic disorder associated with chronic systemic inflammation [9], is a risk factor for several types of cancer, including liver [10], pancreatic [11], endometrial [12], and colorectal [13]. However, data regarding the association between DM and the development of gastric cancer remain conflicting [14–17]. A recent systematic review showed a weak association between DM and gastric cancer with significant between-study heterogeneity [18]. A small Japanese cohort study reported a positive association between hyperglycemia and the risk of gastric cancer [19], but large prospective cohort studies demonstrated such an

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association only in men [14] or only in women [15] and one study showed an inverse association [16].

The inconsistent associations found between DM and gastric cancer may be due to inaccurate assessment of exposure and/or outcome measures in previous studies, including use of self-report data for DM status and use of hospitalization or mortality data for gastric cancer. In addition, although one study included atrophic gastritis as a covariate [20], no previous study has adjusted for intestinal metaplasia, an important risk factor for the development of gastric cancer. Furthermore, all previous cohort studies considered DM as a fixed exposure at baseline, but did not consider new cases of DM during follow-up [21, 22].

Therefore, we examined the prospective association between DM and the risk of developing gastric cancer considering confounders not previously addressed, such as intestinal metaplasia, and also taking into account time-dependent measures of DM in a large cohort of men and women who underwent endoscopic follow-up in a health screening setting.

Materials and methods

Study population

The Kangbuk Samsung Health Study is a cohort study of men and women 18 years of age or older who underwent a comprehensive annual or biennial health examination at the clinics of the Kangbuk Samsung Hospital Total Healthcare Screening Center in Seoul and Suwon, South Korea [23]. Over 80% of participants were employees of various companies and local governmental organizations and their spouses. In South Korea, the Industrial Safety and Health Law requires annual or biennial health screening exams of all employees, offered free of charge. The remaining participants voluntarily paid for screening examinations at the health screening center.

The present analysis included all study participants who participated in at least two screening visits (baseline and at least one follow-up) that included an upper gastrointestinal endoscopy between April 1, 2003 and December 31, 2014 ($n = 195{,}957$; Fig. 1). We excluded participants with gastric cancer identified on upper gastrointestinal endoscopy at baseline ($n = 150$) or those who reported a history of gastric cancer ($n = 492$). We further excluded participants with missing baseline data on fasting glucose ($n = 6$). Because there were participants who had more than one exclusion criteria, the final sample, thus included 195,312 participants (117,610 men and 77,702 women).

The study was approved by the Institutional Review Board of the Kangbuk Samsung Hospital (KBSMC 2015–08-012), which waived the requirement for informed consent as we used only de-identified data obtained during regular health screening exams.

Data collection

Baseline and follow-up examinations were conducted at the clinics of the Kangbuk Samsung Hospital Health Screening Center in Seoul and Suwon, South Korea. At each visit, data regarding demographic characteristics, smoking status, alcohol consumption, medical history, and medication use were collected through standardized self-administered questionnaires. Smoking status was categorized as never, former, or current smoker. Alcohol consumption was categorized as none, moderate (≤ 30 g/day in men and ≤ 20 g/day in women), or high intake (> 30 g/day in men and > 20 g/

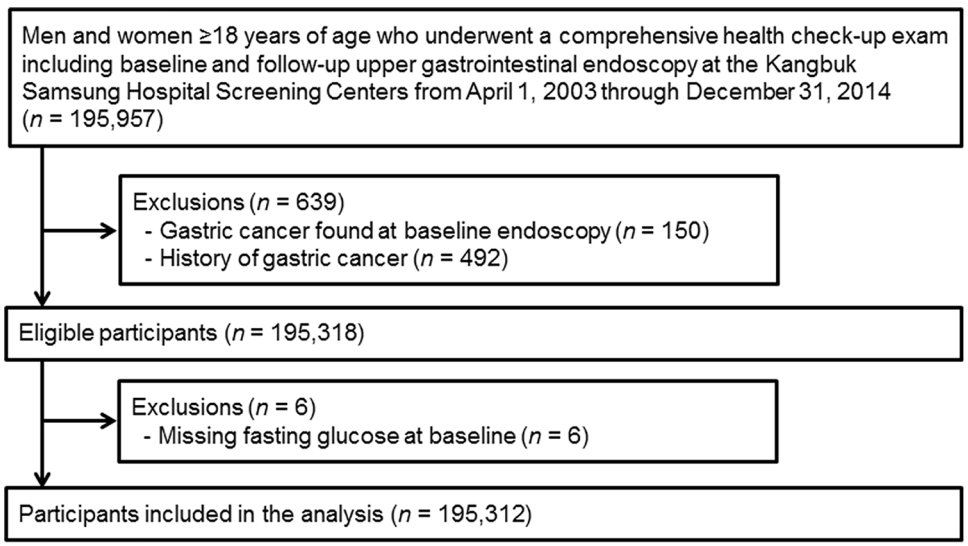

Fig. 1 Study participant flowchart

day in women). Frequency of vigorous physical activity was categorized as 0, 1–3, or > 3 times/week.

Height, weight, and sitting blood pressure were measured by trained nurses. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, self-reported history of hypertension, or current use of antihypertensive medications.

Fasting blood samples were collected after at least 10 h of fasting. Serum fasting glucose levels were measured using the hexokinase method. In the Suwon center, fasting glucose levels were measured on an Advia 1650 analyzer (Bayer Diagnostics, Leverkusen, Germany) until 2009, and on a Modular D analyzer (Roche Diagnostics; Tokyo, Japan) until 2014. In the Seoul center, fasting glucose levels were measured on an Advia 1650 analyzer (Bayer Diagnostics) until 2009, on a Cobas Integra 800 analyzer (Roche Diagnostics; Rotkreuz, Switzerland) until 2012, and on a Modular D analyzer (Roche Diagnostics) until 2014. DM was defined as a fasting serum glucose ≥ 126 mg/dL, a self-reported history of DM, or current use of antidiabetic medications.

Laboratory methods for other analyses have been reported elsewhere [24]. The Laboratory Medicine Department of the Kangbuk Samsung Hospital has been accredited by the Korean Society of Laboratory Medicine (KSLM) and the Korean Association of Quality Assurance for Clinical Laboratories (KAQACL), and participates in the College of American Pathologists (CAP) Survey Proficiency Testing.

Endoscopic examinations were conducted by 13 experienced endoscopists using conventional white light endoscopes (GIF H260, Olympus Medical Systems, Tokyo, Japan). Lidocaine throat spray was applied in all examinees and intravenous midazolam was used according to the examinees' preference. Adequate mucosal visualization was achived in all patients by removing air bubbles and debris using aspiration and mucosal cleansing techniques, as well as adequate air inflation. If remnant food materials hindered mucosal visualization, the examinations was cancelled and rescheduled. All relevant anatomical landmarks, including upper esophageal sphincter, gastroesophageal junction, fundus, gastric body, angle, antrum, and duodenal bulb and second portion were accessed in a standard fashion. During endoscopy, any lesion suggestive of gastric cancer was imaged and described in terms of location, size, and shape. The size of the lesion was measured using open biopsy forceps and the gross appearance was reported according to the Paris classification [25]. Biopsies were taken from all lesions suspicious for malignancy and expert gastrointestinal pathologists evaluated the specimens based on World Health Organization criteria [26]. Gastric cancer was defined as gastric adenocarcinoma or signet ring cell carcinoma. Atrophic gastritis was defined as mucosal thinning with pale and shiny surface and visible submucosal vessels and intestinal metaplasia was defined as nodular elevated whitish plaques in the antrum or corpus [27, 28]. *H. pylori* infection status was evaluated histologically only when indicated such as in the case of peptic ulcer disease, at the discretion of the endoscopist based on Korean guidelines [29].

Statistical analysis

The study endpoint was the development of gastric cancer. Participants were followed from the baseline visit to the visit of gastric cancer diagnosis or to the last available visit. For risk analyses, we estimated the hazard ratio (HR) with 95% confidence interval (CI) for incident gastric cancer, comparing participants with and without diabetes using a spline-based proportional hazards parametric survival model with robust standard errors [30]. These models were used to take into account the interval censoring that arose, because incident gastric cancer occurred at an unknown timepoint between the visit at which gastric cancer was diagnosed by endoscopy and the previous visit. In these models, the baseline hazards were parameterized as restricted cubic splines of log time with three internal knots at the 25th, 50th, and 75th percentiles.

We used three models with increasing degrees of adjustment to account for potential confounding factors at baseline. Model 1 was adjusted for age (continuous), sex, year of initial visit (2004–2005, 2006–2008, 2009–2011, and 2012–2014) and center (Seoul, Suwon). Model 2 was further adjusted for BMI (continuous), smoking (never, former, current, and unknown), alcohol (none, moderate, high, and unknown), physical activity (< 3 times/week, ≥ 3 times/week, and unknown), family history of cancer (yes, no, and unknown), total and high-density lipoprotein (HDL) cholesterol (continuous), triglycerides (continuous), and hypertension (yes, no). In addition to evaluate potential mediation of the association between diabetes and gastric cancer, we fitted an additional model further adjusted for atrophic gastritis and intestinal metaplasia (Model 3). Finally, to evaluate the impact of new cases of diabetes developed over the follow-up period, we conducted additional analyses introducing DM as a time-varying exposure.

We conducted a sensitivity analysis defining DM as a fasting serum glucose ≥ 126 mg/dL, HbA1c ≥ 6.5%, a self-reported history of DM, or current use of antidiabetic medications. Because HbA1c levels were only available between March 1, 2005 and December 31, 2014 (end of study); this analysis was restricted to the participants who had their initial study visit during this period. We also evaluated the association between DM and incident gastric cancer among

the participants who had baseline *H. pylori* status, while adjusting for *H. pylori* positivity at baseline. In addition, we conducted a subgroup analysis by categorizing the participants with DM into those with or without hypoinsulinemia defined as fasting insulin level ≤ 10th percentile of population distribution. All reported *P* values were two-sided and the significance level was set at 0.05. All analyses were performed using STATA version 14 (StataCorp LP, College Station, TX, USA).

Results

The mean (standard deviation) age of study participants was 38.4 (8.0) years, the proportion of men was 60.2%, and the prevalence of DM at baseline was 3.0% ($n = 5,774$; Table 1). Compared to participants without DM, those with DM had a higher BMI and were more likely to be men, smokers, heavy drinkers, and to have hypertension. A higher proportion of atrophic gastritis (43.1 vs. 24.6%, $P < 0.001$) and intestinal

Table 1 Baseline characteristics of study participants

Characteristic	Overall	Normal	Diabetes	*P* value
Participants	195,312	189,538	5,774	
Age, years	38.4 (8.0)	38.2 (7.8)	46.6 (9.7)	< 0.001
Male sex	117,610 (60.2)	113,181 (59.7)	4,429 (76.7)	< 0.001
Family history of cancer	48,268 (24.7)	46,737 (24.7)	1,531 (26.5)	0.001
Body mass index, kg/m^2	23.4 (3.1)	23.3 (3.1)	25.5 (3.3)	< 0.001
Smoking status				< 0.001
Never smoker	100,355 (51.4)	98,329 (51.9)	2,026 (35.1)	
Ex-smoker	33,782 (17.3)	32,197 (17.0)	1,585 (27.5)	
Current smoker	52,293 (26.8)	50,430 (26.6)	1,863 (32.3)	
Unknown	8,882 (4.6)	8,582 (4.5)	300 (5.2)	
Alcohol intake[a]				< 0.001
None	47,855 (24.5)	46,472 (24.5)	1,383 (24.0)	
Moderate	112,685 (57.7)	109,770 (57.9)	2,915 (50.5)	
High	20,690 (10.6)	19,612 (10.4)	1,078 (18.7)	
Unknown	14,082 (7.2)	13,684 (7.2)	398 (6.9)	
Exercise				< 0.001
< 3 times/week	161,146 (82.5)	156,857 (82.8)	4,289 (74.3)	
≥ 3 times/week	30,930 (15.8)	29,600 (15.6)	1,330 (23.0)	
Unknown	3,236 (1.7)	3,081 (1.6)	155 (2.7)	
Metabolic syndrome	31,899 (16.3)	28,198 (14.9)	3,701 (64.1)	< 0.001
SBP, mmHg	112.5 (13.0)	112.3 (12.9)	119.5 (13.5)	< 0.001
DBP, mmHg	72.6 (9.5)	72.4 (9.5)	77.4 (9.4)	< 0.001
Hypertension	24,896 (12.8)	22,589 (11.9)	2,307 (40.0)	< 0.001
Fasting glucose, mg/dL	94.5 (14.1)	93.0 (8.6)	143.0 (43.0)	< 0.001
Fasting insulin, uIU/mL	5.5 (3.9)	5.4 (3.4)	8.2 (12.5)	< 0.001
HOMA-IR	1.3 (1.2)	1.3 (0.8)	3.0 (5.2)	< 0.001
hs-CRP, mg/L	0.04 (0.02, 0.09)	0.04 (0.02, 0.09)	0.08 (0.04, 0.16)	< 0.001
Total cholesterol, mg/dL	193.5 (33.9)	193.2 (33.7)	200.8 (39.7)	< 0.001
Triglycerides, mg/dL	119.6 (80.2)	117.7 (77.6)	178.8 (126.0)	< 0.001
LDL cholesterol, mg/dL	114.8 (30.3)	114.6 (30.2)	119.7 (34.4)	< 0.001
HDL cholesterol, mg/dL	56.0 (13.2)	56.1 (13.2)	50.4 (11.8)	< 0.001
H. pylori positive	19,083/22,793 (83.7)	18,279/21,828 (83.7)	804/965 (83.3)	0.730
Atrophic gastritis	49,171 (25.2)	46,684 (24.6)	2,487 (43.1)	< 0.001
Intestinal metaplasia	14,280 (7.3)	13,488 (7.1)	792 (13.7)	< 0.001

Data in table are mean (standard deviation), number (percentage), or median (25th and 75th percentiles)

DBP diastolic blood pressure, *HDL* high-density lipoprotein, *HOMA-IR* homeostatic model assessment-insulin resistance, *hs-CRP* high-sensitivity C-reactive protein, *LDL* low-density lipoprotein, *SBP* systolic blood pressure

[a]Moderate intake: ≤ 30 g/day in men and ≤ 20 g/day in women; high intake: > 30 g/day in men and > 20 g/day in women

metaplasia (13.7 vs. 7.1%, $P<0.001$), were found among participants with DM than among those without DM. The baseline *H. pylori* status was evaluated in 22,793 (11.6%) participants and among them, 19,803 (83.7%) had positive results. The proportions of *H. pylori* infection were not different between participants with DM and those without DM ($P=0.730$).

During 865,511 person-years of follow-up (median follow-up 4.4 years), 198 participants developed incident gastric cancer. The histopathology was only available from the biopsy results. They showed that 31.3% (62/198) were differentiated-type cancers (well or moderately differentiated adenocarinoma), 59.6% (118/198) were undifferentiated-type cancers (poorly differentiated adenocarcinoma, signet ring cell carcinoma, or mucinous adenocarcinoma), and 9.1% (18/198) were unclassified adenocarciomas. The information on disease stage was available only for 175 (88.4%). Among them, 83.4% (146/175) had localized disease, 15.4% (27/175) had regional disease, and only 1.1% (2/175) had distant metastasis.

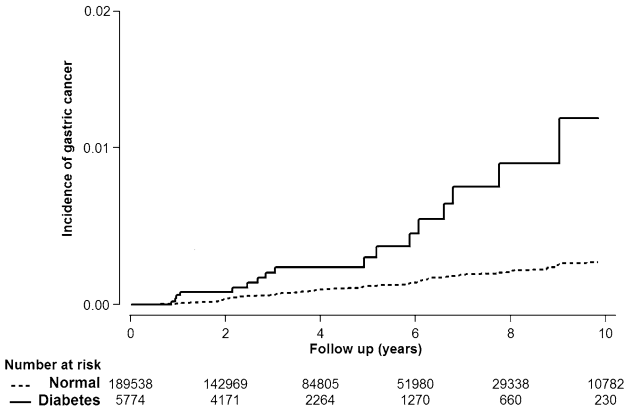

Fig. 2 Cumulative incidence of gastric cancer by presence of diabetes mellitus at baseline

The cumulative incidence of gastric cancer was consistently higher in participants with DM than in those without DM throughout follow-up (Fig. 2). The age-, sex-, year of visit- and center-adjusted HR for incident gastric cancer comparing participants with and without DM was 1.80 (95% CI 1.07, 3.01; $P=0.026$; Table 2). This association was essentially unchanged after adjusting for BMI, smoking, alcohol, physical activity, family history of cancer, total and HDL cholesterol, triglycerides, atrophic gastritis, and intestinal metaplasia (HR 1.76, 95% CI 1.04–2.97; $P=0.033$). Evaluation of the association between incident DM and gastric cancer with DM as a time-varying covariate in fully adjusted models found that the HR for gastric cancer comparing participants with and without DM was 1.66 (95% CI 1.04–2.68; $P=0.036$).

The association between DM and incident gastric cancer did not differ by the presence of intestinal metaplasia (P for interaction = 0.61; Supplementary Table 1). Cross-classification of study participants by the presence of DM and intestinal metaplasia at baseline showed that the risk of gastric cancer in participants with both DM and intestinal metaplasia was substantially higher than the risk in participants with neither condition (HR 5.08, 95% CI 2.30–11.19; $P<0.001$; Fig. 3, Supplementary Table 2).

The sensitivity analysis using a definition of DM which additionally incorporated HbA1c ≥ 6.5% resulted in a similar magnitude of the association between DM and the risk of gastric cancer (fully adjusted HR 1.66, 95% CI 0.95–2.92; $P=0.076$) (Supplementary Table 3). Among the participants with baseline *H. pylori* status, the association between DM and incident gastric cancer was similar before (HR 2.14, 95% CI 0.86–5.33; $P=0.100$), and after adjustment for *H. pylori* status (HR 2.12, 95% CI 0.84–5.28; $P=0.110$) (Supplementary Table 4). In the subgroup analysis according to

Table 2 Hazard ratios for incident gastric cancer by diabetes mellitus status

	Person-years	No. of cases	Incidence rate (per 100,000 person-years)	Crude HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Baseline diabetes							
No	842,395.4	181	21.5	Reference	Reference	Reference	Reference
Yes	23,115.9	17	73.5	3.54 (2.15, 5.82)	1.80 (1.07, 3.01)	1.79 (1.06, 3.03)	1.76 (1.04, 2.97)
P value				<0.001	0.026	0.029	0.033
Time-dependent diabetes							
No	835,336.8	177	22.2	Reference	Reference	Reference	Reference
Yes	30,153.9	21	69.6	3.12 (1.98, 4.91)	1.70 (1.06, 2.71)	1.69 (1.03, 2.72)	1.66 (1.04, 2.68)
P value				<0.001	0.033	0.032	0.036

Model 1 adjusted for age, sex, year of visit, and center; Model 2 further adjusted for body mass index, smoking, alcohol, physical activity, family cancer history, total and HDL cholesterol, triglycerides, and hypertension; Model 3 further adjusted for endoscopically diagnosed atrophic gastritis and intestinal metaplasia

CI confidence interval, *HR* hazard ratio

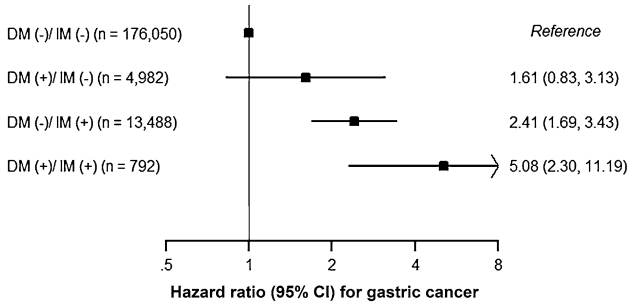

Fig. 3 Hazard ratios for gastric cancer according to joint presence of diabetes mellitus and intestinal metaplasia at baseline. Hazard ratios adjusted for age, sex, year of visit, center, body mass index, smoking, alcohol, physical activity, family cancer history, total and HDL cholesterol, triglycerides, and hypertension. *DM* diabetes at baseline, *IM* intestinal metaplasia

the presence of hypoinsulinemia, HR (95% CI) for incident gastric cancer comparing DM without hypoinsulinemia and DM with hypoinsulinemia to no DM as a reference were 1.79 (1.02–3.11) and 2.20 (0.53–9.07), respectively (*P* for trend = 0.023) (Supplementary Table 5).

Discussion

In this large study involving almost 200,000 men and women who underwent repeated upper endoscopic examinations, participants with DM were at increased risk of developing gastric cancer even after adjustment for multiple potential confounders and for atrophic gastritis and intestinal metaplasia. The observed association was very similar when newly developed DM during follow-up was considered as a time-varying covariate, indicating that the increased risk of gastric cancer in DM begins relatively early in the course of the disease.

Previous cohort studies with a large sample size that examined the association between DM and gastric cancer identified cancer cases by means of cancer registries or hospital admission data, which are prone to misclassification, incomplete ascertainment, and delayed reporting [14–16, 31]. Furthermore, these studies could not rule out the presence of prevalent subclinical gastric cancer at baseline. In the present study, all participants were evaluated with upper endoscopy at baseline and during follow-up by experienced endoscopists. We could thus exclude participants with gastric cancer at baseline, minimizing reverse causation, and misclassification bias.

In this study, we determined DM status on the basis of both laboratory analysis of fasting glucose and medical history. In contrast, several previous investigations of the association between DM and gastric cancer used only self-administered questionnaires [15, 16], with limited sensitivity and specificity [32]. This factor could explain our finding of a stronger association between DM and gastric cancer than that in prior Japanese and Korean cohort studies, as well as a systematic review of this topic [14, 15, 18, 33].

Our results are consistent with the findings of a community-based prospective cohort study from Japan, which showed that hyperglycemia was a risk factor for the development of gastric cancer independent of *H. pylori* seropositivity [19], as well as with the findings of another study from Japan, in which DM was a risk factor for gastric cancer independent of atrophic gastritis [20]. We further showed that DM is a risk factor for gastric cancer independent of intestinal metaplasia and when new cases of DM are considered as a time-varying exposure during follow-up.

DM is an established risk factor for several types of cancer, particularly liver and pancreatic cancers [10, 11]. Several mechanisms may underlie the association between DM and the development of various cancers, including gastric cancer. Hyperglycemia can cause DNA damage directly [34] or can lead to damage through the production of reactive oxygen species [35]. Metabolically induced oxidative stress may result in the accumulation of mutations in oncogenes and tumor suppressor genes [36]. In particular, the role of oxidative DNA damage in gastric carcinogenesis may explain a synergistic interaction between hyperglycemia and *H. pylori* infection [19, 36]. Hyperinsulinemia and elevated levels of insulin-like growth factors (IGFs) in DM could also contribute to cancer development. Previous studies have reported that obesity is associated with gastric cardiac cancer [37, 38]. Insulin resistance and consequent hyperinsulinemia were suggested as the possible mechanisms. Although obesity was not directly related to non-cardiac gastric cancer, insulin resistance may still play a role in gastric carcinogenesis in relation to DM. Overexpression of IGFs and heterogeneous expression of IGF-binding proteins (IGFBPs) may play a pivotal role in gastric cancer development, growth, and metastasis [39, 40]. Hyperinsulinemia may also downregulate IGFBP levels, indirectly contributing to elevated levels of IGF [41].

Intestinal metaplasia is also an established risk factor for gastric cancer [8]. In the present study, participants with both DM and intestinal metaplasia had an almost fivefold risk of developing gastric cancer compared to those with neither DM nor metaplasia. It has been suggested that subjects with intestinal metaplasia may benefit from annual endoscopic screening for gastric cancer, rather than the biennial screening recommended for average-risk individuals [8]. Our findings suggest that endoscopic screening should be particularly intensive in subjects with both DM and metaplasia. Further research is needed to individualize the interval for gastric cancer screening in this high-risk population.

The present study has multiple strengths, including the large sample size, the availability of endoscopic data at

baseline and during follow-up, the pathologic confirmation of cases of gastric cancer, the availability of fasting glucose levels and other information regarding DM at baseline and during follow-up, and the availability of high-quality data on multiple demographic, lifestyle, medical history, and examination variables. Furthermore, our study population is comprised of middle-aged men and women who are less likely than older cohorts to be subjected to selection bias and biases due to mortality, comorbidities, and medication use.

Several limitations of our study, however, need to be considered in the interpretation of our results. First, we did not include HbA1c levels in the definition of DM in the main analysis, because HbA1c was not measured until after March 2005 in our cohort. In the sensitivity analysis with a different definition of DM incorporating HbA1c levels, the magnitude of the association was similar to that from the main analysis although, it lost statistical significance because of shorter follow-up duration and smaller number of events. There is a risk of false positive DM if participant had failed to adhere to the fasting time. However, we believe that it is unlikely that participants did not comply with the fasting time, because they underwent upper endoscopy at the same day of blood tests during the health checkup. Nevertheless, if they had failed to adhere to fasting time, this would have led to the dilution of the association between DM and the risk of gastric cancer. Second, we had information on *H. pylori* infection status only in a small proportion of participants because *H. pylori* testing was performed at the discretion of the endoscopists. However, baseline endoscopic information on the presence of atrophic gastritis and intestinal metaplasia was available for all participants. Atrophic gastritis and intestinal metaplasia are intermediate factors representing chronic *H. pylori* infection and serve as surrogate variables to control for the increased risk of gastric cancer associated with *H. pylori* infection. Furthermore, we could not link our data to information on *H. pylori* eradication, because we used only de-identified data routinely collected during health screening visits. Further study is required to evaluate whether the association between DM and gastric cancer may differ according to *H. pylori* eradication status. Third, we diagnosed atrophic gastritis and intestinal metaplasia using white light endoscopy. Because white light endoscopy has low sensitivity in the diagnosis of intestinal metaplasia, the use of narrow band imaging might have improved the accuracy of the diagnosis and minimized potential misclassification [42]. Fourth, despite the high accuracy of upper endoscopy in the diagnosis of gastric cancer, it is possible that some cases were missed [43]. In rare diseases, however, missing some of the outcomes (reduced sensitivity) has a very small impact on the HR and in any case would tend to underestimate the association. Finally, our study was based on apparently healthy Korean men and women who regularly attended health screening exam visits. Our findings may not generalize to other races/ethnicities or to other settings.

In conclusion, in this large cohort study with endoscopic follow-up, we found that DM was independently associated with an increased risk of developing gastric cancer. This increased risk was independent of mucosal atrophy and of intestinal metaplasia and consistent in participants who developed new cases of diabetes during follow-up. Our findings suggest that patients with DM may require more intensive endoscopic follow-up, but additional research is needed to develop individualized follow-up guidelines for these patients.

Author contributions HJY has contributed to conception and design of study, interpretation of data and drafting of the manuscript. DK has contributed to design of study, analysis and interpretation of data, and drafting of the manuscript. YC has contributed to conception and design of study, analysis and interpretation of data and critical revision of the manuscript for important intellectual content. JA has contributed to acquisition of data and critical revision of the manuscript for important intellectual content. SR has contributed to conception and design of study, analysis and interpretation of data and critical revision of the manuscript for important intellectual content. JC has contributed to conception and design of study, interpretation of data and critical revision of the manuscript for important intellectual content. EG has contributed to conception and design of study, interpretation of data and critical revision of the manuscript for important intellectual content. CIS has contributed to conception of study, acquisition of data, and critical revision of the manuscript for important intellectual content.

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Compliance with ethical standards

Conflict of interest No potential conflicts of interest were disclosed.

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