Research Article

Cancer Epidemiology, Biomarkers & Prevention

Prospective Study of Self-Reported Diabetes and Risk of Upper Gastrointestinal Cancers

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Abstract

Background: Although gastric noncardia adenocarcinoma (GNCA) incidence rates in the United States have decreased, the rates of gastric cardia adenocarcinoma (GCA) and esophageal adenocarcinoma (EADC) have increased. Obesity increases the risks of GCA and EADC, and the associations may be partially mediated by insulin resistance. A few case-control studies have shown an association between diabetes and an increased risk of EADC.

Methods: We prospectively examined the association between diabetes and upper gastrointestinal (UGI) cancers in a cohort of 469,448 people in the United States, ages 50 to 71 at baseline. Cox proportional hazards regression was used to estimate the HR and 95% CI for diabetes and UGI cancers, controlling for multiple potential confounders, including body mass index (BMI).

Results: We observed no association of self-reported diabetes with risk of EADC, HR (95% CI) = 0.98 (0.73–1.31), esophageal squamous cell carcinoma (ESCC), HR (95% CI) = 1.02 (0.60–1.74), or GNCA, HR (95% CI) = 0.98 (0.70–1.37). However, diabetes was significantly associated with an increased risk of GCA, HR (95% CI) = 1.89 (1.43–2.50). The significant association between diabetes and risk of GCA remained after adjustment for BMI, HR (95% CI) = 1.70 (1.28–2.26) and did not differ by BMI strata ($P_{\text{interaction}} = 0.83$). The significant association was unchanged when restricting to only overweight subjects (BMI 25 to $\leq$30), HR (95% CI) = 1.83 (1.18–2.85).

Conclusions: We found a significant association between self-reported diabetes and increased risk of GCA.

Impact: Our results suggest that the metabolic and hormonal changes related to diabetes may play a role in the etiology of GCA independently from BMI. *Cancer Epidemiol Biomarkers Prev; 20(5); 954–61. ©2011 AACR.*

Introduction

Diabetes and cancer are prevalent diseases with increasing incidence. Recently, results from a series of studies and meta-analyses have indicated that some cancers develop more commonly in patients with diabetes (1). Type 2 diabetes is associated with increased risk of several cancer types, including non-Hodgkin lymphoma (2), postmenopausal breast (3), colorectal (4), endometrial (5), liver (6), bladder (7), and pancreatic (8) cancers, whereas prostate cancer (9) occurs less often in men with diabetes. Some of these associations appear to be independent of body mass index (BMI; ref. 10). Few studies to date have examined links with Type 1 diabetes, usually an early-onset autoimmune disease that is relatively rare compared with Type 2 diabetes; due to physiologic differences, Type 1 and Type 2 diabetes may have different associations with cancer risk.

Type 2 diabetes and cancer share some similar risk factors, including obesity and a sedentary lifestyle. Characterized by hyperinsulinemia, Type 2 diabetes involves a loss of glucose homeostasis or the inability of tissues to respond to insulin. The chronic increase in circulating glucose and lipids may in turn further impair insulin secretion, and the aberrations in the insulin-like growth factor pathways and steroid hormone metabolism may play a role in predisposing diabetics to cancer. Hyperinsulinemia may promote cancer in diabetic patients because insulin is a growth factor with metabolic as well as mitogenic effects. Obesity, hyperglycemia, and increased oxidative stress may act together to contribute to the increase in cancer risk among diabetics.

In the United States, the incidence of esophageal adenocarcinoma (EADC) has risen 350% since the mid-1970s (11–13), and to a lesser extent, the incidence of gastric cardia adenocarcinoma (GCA) has also increased (14), although improved cancer site classification may largely account for the increase (15). By contrast, the incidence rates of esophageal squamous cell carcinoma (ESCC) and gastric noncardia adenocarcinoma (GNCA)

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have decreased (13, 15, 16). The increase of EADC is concordant with the increasing prevalence of obesity, and adiposity has been a consistent risk factor for EADC. Obesity may increase intraabdominal pressure, with a mechanical effect on the lower esophageal sphincter that predisposes to gastroesophageal reflux disease (GERD); however, some studies have shown that obesity is associated with EADC even in the absence of reflux (17, 18). Thus, insulin resistance, which results from the metabolic and hormonal changes of obesity, may be a risk factor for cancers of the gastroesophageal junction. Here, we prospectively examined the association between self-reported diabetes and UGI cancers using the NIH-AARP Diet and Health Study cohort.

Materials and Methods

Study population

The details of the NIH-AARP Diet and Health study have been described elsewhere (19). Briefly, between 1995 and 1996, a questionnaire was mailed to 3.5 million AARP members who were between 50 and 71 years of age and residing in 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia and Detroit, Michigan). The questionnaire elicited information on demographic characteristics, dietary intake, and health-related behaviors. Out of the 617,119 people who completed and returned the questionnaire, 566,402 completed the questionnaire in satisfactory detail and consented to be in the study. We excluded proxy-responders (15,760), subjects with a cancer prior to baseline (51,234), those with calorie intake of more than 2 interquartile ranges from the median (4,417), those with unknown BMI or diabetes status (12,523), and those who died or were diagnosed with cancer on the first day of follow-up (12). Because concerns about reverse causation, those subjects with less than 2 years of follow-up were also excluded (13,020). The resulting cohort included 469,448 participants: 280,883 men and 188,565 women.

Follow-up and case ascertainment

We calculated follow-up time from 2 years after the day of study entry until diagnosis of an upper gastrointestinal cancer, death, or the current end of follow-up (December 31, 2006). The cohort database was matched annually to that of the National Change of Address (NCOA) maintained by the US Postal Service (USPS) so that the address of each cohort member could be updated. Annual linkage of the cohort to the Social Security Administration Death Master File (SSA DMF) on deaths in the United States, searches of the National Death Index (NDI), and linkage to cancer registries were performed to ascertain vital status.

Cancer cases were identified by cancer registries in the original 8 states or metropolitan areas and 2 additional states (Arizona and Texas); cancers were identified by anatomic site and histologic code of the International Classification of Disease for Oncology, 3rd edition (ICD-O). Tumors with site codes C15.0 to 15.9 were esophageal cancer, and ESCC and EADC were identified by histology; tumors with site code C16.0 and adenocarcinoma histology were classified as GCA; and tumors with site codes C16.1 to 16.9 and adenocarcinoma histology or those without a specified location were categorized as GNCA.

Exposure assessment

All exposure variables were derived from the information provided in the baseline questionnaire, which inquired about demographics, tobacco and alcohol use, physical activity, and diet using a 124-item food frequency questionnaire (19). History of diabetes was assessed with the question, "Have you ever been told by a doctor that you had diabetes?" BMI was calculated from self-reported baseline height and weight and was categorized as 5 quantiles based on WHO standard definitions: <18.5, 18.5 to <25, 25 to <30, 30 to <35, and $\geq$35 kg/m^2. Calories were assessed as kcal per day. Fruit and vegetable intake were measured separately as nonalcohol energy-adjusted pyramid equivalents per day. Alcohol consumption was measured as drinks per day, and tobacco smoking was categorized as: never smokers, former smokers of $\leq$20 cigarettes/day, former smokers of >20 cigarettes/day, current smokers of $\leq$20 cigarettes/day, and current smokers of >20 cigarettes/day. Participants were grouped into 4 race and ethnicity categories: white, not Hispanic; black, not Hispanic; Hispanic; and Asian, Pacific Islander, and American Indian/Alaska Native. Education was categorized into 4 ordinal categories: high school graduate or less, technical school or some college, college graduate, and post-graduate education. We included 2 physical activity variables: usual physical routine throughout the day and vigorous physical activity at baseline. Activity throughout the day included: sit all day, sit much of the day/walk some times, stand/walk often/no lifting, lift/carry light loads, and carry heavy loads. Vigorous physical activity included: never, rarely, 1 to 3 times/month, 1 to 2 times/week, 3 to 4 times/week, 5 or more times per week. Missing indicator variables were used for those who had missing values.

Statistical analysis

All analyses were conducted using SAS (SAS Institute). We interpreted $P < 0.05$ and 95% CIs excluding 1 as statistically significant. We used multivariate Cox proportional hazards models to estimate HR and 2-sided 95% CIs for self-reported history of diabetes. Variables considered a priori as important potential confounders were included in the models, and we show both age-adjusted and multivariate-adjusted effect estimates. To detect deviations from the proportional hazards assumption, we examined potential differential effects by follow-up time by fitting the models using cases from each individual year of follow-up.

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We examined the association between self-reported history of diabetes and UGI cancers separately in men and women. We examined the association with and without adjusting for continuous BMI and the WHO categories of BMI. We also fit separate models in BMI strata that contained ≥10 cancer cases each. In addition, to increase the comparability across studies, we examined the association when the obese and extremely obese categories (BMI 30–<35 and BMI 35+, respectively) were combined as BMI ≥30. We tested for effect modification (interaction) using cross-product terms and modeled BMI as a continuous variable for this purpose.

Results

Among the eligible cohort of 469,448 participants, 41,388 (8.82%) reported a diabetes diagnosis. Table 1 presents the cohort characteristics by diabetes status. More men than women reported having a history of diabetes. Overall, diabetics were older, had higher BMI and higher caloric intake, drank less alcohol, were more likely to have smoked, had less education, and were less physically active than nondiabetics. The diabetics group had higher percentages of non-whites than the nondiabetics group. Among the cohort, we identified 534 EADC, 172 ESCC, 352 GCA, and 379 GNCA incident cases. The average length of follow-up was 7.96 years. Table 2 presents the case counts and age-adjusted and multivariate-adjusted HRs and 95% CIs for the associations between self-reported diabetes and risk of EADC, ESCC, GCA, and GNCA for the whole cohort and for men and women separately. Although no significant associations were observed between self-reported diabetes and EADC, ESCC, and GNCA, there was significantly increased risk for GCA. The risk estimates for ESCC, EADC, and GNCA were null among both men and women. We had low power to assess the risk estimates for each cancer site among women because fewer cases occurred among women, so the risk estimates for women had larger CIs and may be considered exploratory. We found no evidence for effect modification by sex: for ESCC, $P_{\text{interaction}} = 0.60$; EADC, $P_{\text{interaction}} = 0.68$; GCA, $P_{\text{interaction}} = 0.95$, and GNCA, $P_{\text{interaction}} = 0.30$.

Figure 1 presents the overall risk estimates from the cohort before and after adjustment for BMI and by strata of WHO-defined BMI categories. Additional adjustment for BMI only marginally changed the risk estimates. Also, the risk estimates for all the strata of BMI remained null for ESCC, EADC, and GNCA. The risk estimates for GCA remained similarly elevated among participants who were in each of the WHO-defined BMI categories. When we considered participants with BMI ≥30 as a single category, we observed the following results: ESCC, HR 0.41, 95% CI 0.10 to 1.74; EADC, HR 1.08, 95% CI 0.72 to 1.62; GCA, HR 1.51, 95% CI 0.98 to 2.33; and GNCA, HR 0.84, 95% CI 0.48 to 1.47. We found no evidence for effect modification by BMI: for ESCC, $P_{\text{interaction}} = 0.56$; EADC, $P_{\text{interaction}} = 0.89$; GCA, $P_{\text{interaction}} = 0.83$; GNCA, $P_{\text{interaction}} = 0.53$.

Discussion

We found a significant association between self-reported diabetes and an increased risk of GCA, which was independent of BMI. We saw no clear association between self-reported diabetes and risk of EADC, ESCC, or GNCA.

Few studies have examined the association between diabetes and UGI cancers, and inconsistent associations have been observed. A case-control study of US veterans with GERD found no evidence of an association between diabetes and EADC or GCA (20). Another case-control study of British women found that diabetes was non-significantly associated with an increased risk of EADC (21). However, a case-control study from Australia found a significantly increased risk of EADC associated with diabetes (22). In contrast to the risk estimates in our study that were independent of BMI, the risk estimates observed in both the Australian and British studies were attenuated on adjusting for BMI (21, 22).

Although our large prospective study examined the association between diabetes and the histologic subsites of esophageal and stomach cancers, some other studies did not differentiate the subsites. For example, a study that used the Swedish national registries found that patients discharged from the hospital for Type 2 diabetes had increased risks of esophageal and stomach cancers (23) but did not specify the risks for the histologic subsites. In Japan, a case-control study found increased risks of esophageal and stomach cancers among diabetic men and women, respectively (24), and a large prospective cohort study found a significantly increased risk of stomach cancer associated with diabetes in women (25), but neither study specified the subsites.

The mechanistic link between diabetes and gastric cancer has been explored in diabetic mice, which have been shown to be more susceptible to chemical induction of gastric carcinogenesis (26).

Inflammation has been implicated as an important etiologic factor in both insulin resistance and Type 2 diabetes (27), and chronic inflammation also plays a role in the development of gastric atrophy and cancer (28). Interestingly, over the past 2 decades, bariatric surgeons have recognized that gastric bypass surgery, particularly total gastrectomy and to a lesser extent gastric binding, causes a durable improvement in Type 2 diabetes; remarkably, the normalization of glucose metabolism occurs within several weeks of surgery, long before any substantial weight loss occurs (29). This amelioration of diabetes has been shown consistently in obese patients (29–31) undergoing gastric bypass surgery and somewhat consistently in patients undergoing surgery for other indications, such as gastric cancer or gastric ulcer disease (32–34). In particular, bypass surgery alters the dietary exposure of the gastric cardia tissue. Therefore,

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Table 1. NIH-AARP Study of Diet and Health cohort subject characteristics overall and by diabetes status

Characteristic	Whole cohort	Nondiabetic	Diabetic
n (%)	469,448	428,060 (91.18)	41,388 (8.82)
Female sex, *n* (%)	188,565 (40.17)	175,060 (40.90)	13,505 (32.63)
Age at entry (years), mean (SD)	61.98 (5.37)	61.90 (5.39)	62.81 (5.14)
BMI (kg/m^2), mean (SD)	27.10 (4.81)	26.83 (4.63)	29.83 (5.72)
<18.5 (underweight), *n* (%)	4,417 (0.94)	4,206 (0.98)	211 (0.51)
18.5–<25 (normal weight), *n* (%)	161,582 (34.42)	154,381 (36.07)	7,201 (17.40)
25–<30 (overweight), *n* (%)	200,267 (42.66)	183,671 (42.91)	16,596 (40.10)
30–<35 (obese), *n* (%)	73,974 (15.76)	63,216 (14.77)	10,758 (25.99)
≥35 (obese), *n* (%)	29,208 (6.22)	22,586 (5.28)	6,622 (16.00)
Calories intake (kcal/day), mean (SD)	1835.79 (803.92)	1835.05 (801.38)	1843.40 (829.68)
Fruit (servings/day), mean (SD)	1.19 (0.81)	1.19 (0.81)	1.18 (0.79)
Vegetables (servings/day), mean (SD)	1.13 (0.59)	1.13 (0.59)	1.15 (0.59)
Alcohol (drinks/day), mean (SD)	0.91 (2.37)	0.94 (2.40)	0.56 (2.01)
Smoking[a]			
Never, *n* (%)	165,659 (36.64)	152,910 (37.09)	12,749 (32.01)
Former, ≤20 cigs/d, *n* (%)	125,566 (27.77)	114,882 (27.86)	10,684 (26.83)
Former, >20 cigs/d, *n* (%)	97,636 (21.59)	86,051 (20.87)	11,585 (29.09)
Current, ≤20 cigs/d, *n* (%)	40,958 (9.06)	38,109 (9.24)	2,849 (7.15)
Current, >20 cigs/d, *n* (%)	22,309 (4.93)	20,352 (4.94)	1,957 (4.91)
Race[a]			
White, not Hispanic, *n* (%)	429,375 (92.63)	393,673 (93.10)	35,702 (87.69)
Black, not Hispanic, *n* (%)	17,641 (3.81)	14,709 (3.48)	2,932 (7.20)
Hispanic, *n* (%)	8,878 (1.92)	7,686 (1.82)	1,192 (2.93)
Asian, Pac Isl, Am Indian/Alaska Native *n* (%)	7,659 (1.65)	6,769 (1.60)	890 (2.19)
Education[a]			
High school graduate or less, *n* (%)	118,035 (25.87)	105,347 (25.31)	12,688 (31.71)
Technical/some college, *n* (%)	155,472 (34.08)	141,137 (33.91)	14,335 (35.83)
College graduate, *n* (%)	89,083 (19.52)	82,245 (19.76)	6,838 (17.09)
Postgraduate, *n* (%)	93,668 (20.53)	87,526 (21.03)	6,142 (15.35)
Activity throughout the day[a]			
Sit during day, not much walking, *n* (%)	36,489 (7.95)	31,678 (7.56)	4,811 (11.96)
Sit much of the day, walk a fair amount, *n* (%)	151,173 (32.92)	136,653 (32.62)	14,520 (36.09)
Stand/walk a lot, no lifting, *n* (%)	177,038 (38.55)	162,459 (38.78)	14,579 (36.24)
Lift carry light loads, *n* (%)	80,932 (17.62)	75,502 (18.02)	5,430 (13.50)
Heavy work, *n* (%)	13,560 (2.95)	12,669 (3.02)	891 (2.21)
Vigorous physical activity[a]			
Never, *n* (%)	19,895 (4.28)	16,803 (3.96)	3,092 (7.57)
Rarely, *n* (%)	62,823 (13.52)	55,233 (13.03)	7,590 (18.58)
1–3/mo, *n* (%)	63,664 (13.70)	58,069 (13.70)	5,595 (13.70)
1–2/wk, *n* (%)	101,366 (2.18)	93,220 (21.99)	8,146 (19.95)
3–4/wk, *n* (%)	126,406 (27.20)	116,723 (27.54)	9,683 (23.71)
5+/wk, *n* (%)	90,567 (19.49)	83,833 (19.78)	6,734 (16.49)

[a]Participants with missing values for these variables were excluded from this table. Smoking: 17,320 excluded; race: 5,895 excluded; education: 13,190 excluded; activity throughout the day: 10,256 excluded; vigorous physical activity: 4,727 excluded.

the hormonal changes as a result of gastrectomy in bypass surgery may be implicated in changes in glucose metabolism (35, 36).

Diabetes may be in the causal pathway between higher BMI and cancer risk. Therefore, we modeled the association between diabetes and cancer risk with and without adjusting for BMI and also across BMI strata. We found no significant association between diabetes and risk for ESCC, EADC, and GNCA, but a significantly increased risk for GCA. The minimal change in the estimate of the effect of diabetes on GCA risk after adjustment for BMI and the similarity of effect of diabetes in different BMI strata suggest that the effect of diabetes is independent of BMI.

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Table 2. Association between self-reported diabetes and UGI cancers

	Cancer	Nondiabetics, *n*	Diabetics, *n*	Age-adjusted HR (95% CI)	Multivariate-adjusted[a] HR (95% CI)
Entire cohort	ESCC	157	15	1.03 (0.60–1.74)	1.02 (0.60–1.74)
	EADC	482	52	1.16 (0.87–1.54)	0.98 (0.73–1.31)
	GCA	291	61	2.23 (1.69–2.94)	1.89 (1.43–2.50)
	GNCA	340	39	1.20 (0.86–1.68)	0.98 (0.70–1.37)
Males only	ESCC	103	12	1.11 (0.61–2.01)	1.08 (0.59–1.98)
	EADC	446	50	1.06 (0.79–1.42)	1.00 (0.74–1.34)
	GCA	256	56	2.07 (1.55–2.76)	1.89 (1.41–2.54)
	GNCA	239	27	1.05 (0.71–1.57)	0.90 (0.60–1.34)
Females only	ESCC	54	3	0.74 (0.23–2.35)	0.87 (0.27–2.82)
	EADC	36	2	0.75 (0.18–3.13)	0.68 (0.16–2.85)
	GCA	35	5	1.83 (0.72–4.67)	1.77 (0.68–4.58)
	GNCA	101	12	1.53 (0.84–2.78)	1.24 (0.67–2.28)

[a]Potential confounders for the entire cohort models included age, sex, calories, alcohol consumption, smoking, fruit consumption, vegetable consumption, ethnicity, education, and physical activity; confounders for the males only or females only models included all these variables except sex.

The significant association between diabetes and GCA could reflect reverse causality because undiagnosed cancer may have induced diabetes. To limit this potential problem, we excluded the first 2 years of follow-up after the completion of the baseline questionnaire. In fact, we performed multiple subanalyses to examine a potential latency effect, but we found no effect between early and late follow-up (beyond 6 years of follow-up). In addition, a diagnosis of diabetes may increase vigilance and medical care and subsequently, the diagnosis of cancer. Yet, if this was the issue, we would expect to find an increased risk for the other cancer sites as well.

The significant association found between diabetes and GCA, but not EADC, GNCA, or ESCC, could also reflect a chance finding. However, the etiologies of the UGI cancer histologic subsites have been shown to be different. For example, BMI $\geq$35 was shown to be significantly associated with increased risks for EADC and GCA, but not for GNCA (37). In addition, infection with *Helicobacter pylori* (*H. pylori*), but not gastric atrophy, is associated with a reduced risk of EADC, whereas the opposite seems to be true for GCA, and both infection and gastric atrophy may be associated with increased risk of ESCC (38–40).

This study has many strengths. The prospective design avoided exposure recall bias and included a very large sample size, over 450,000 participants, almost 9% of whom had self-reported diabetes. The baseline questionnaire assessed many potential confounding factors; however, unmeasured residual confounding may still be a possibility. An additional strength of this study was the ability to examine site-specific UGI cancers separately.

This study also had some limitations. Self-reported diabetes may be biased because participants may not be aware of their disease status. Nonetheless, self-reported diabetes is a robust exposure measure; recent studies in the United States on the concordance between patient self-report of diabetes and medical record audits have found excellent agreement of greater than 92% and κ scores of greater than 0.80 (41, 42). Although the questionnaire used in this study did not specify Type 1 or Type 2 diabetes, we expected that the majority of self-reported diabetes were Type 2; according to the National Institute of Diabetes and Digestive and Kidney Diseases, 90% to 95% of diabetes in the United States are Type 2 (43). Nonetheless, a previous cohort study of patients hospitalized for Type 1 diabetes found an elevated risk of stomach cancer (44). Our study used self-reported diabetes assessed at baseline and did not have follow-up information regarding the diabetes status of those who were nondiabetic at baseline. If nondiabetics developed diabetes after the baseline assessment, the potential misclassification may bias the results toward the null.

We were limited by the information provided by the NIH-AARP Diet and Health Study baseline questionnaire. Therefore, we could not consider alternative measurements of obesity such as waist-to-hip ratio. We did not have information on *H. pylori* infection status, which may have been important because *H. pylori* gastritis has been suggested to enhance glucose-stimulated insulin release by increasing gastrin secretion (45). Furthermore, we did not have information on the use of antidiabetic drugs. Unfortunately, we did not have information on the duration of diabetes, which may be important as a previous Australian case-control study found an increased risk of esophageal adenocarcinoma among those who had a history of diabetes for $\geq$10 years (22).

We examined the effect of some potential confounders for which we had information for only a subset of the cohort. For example, GERD may play a role in the

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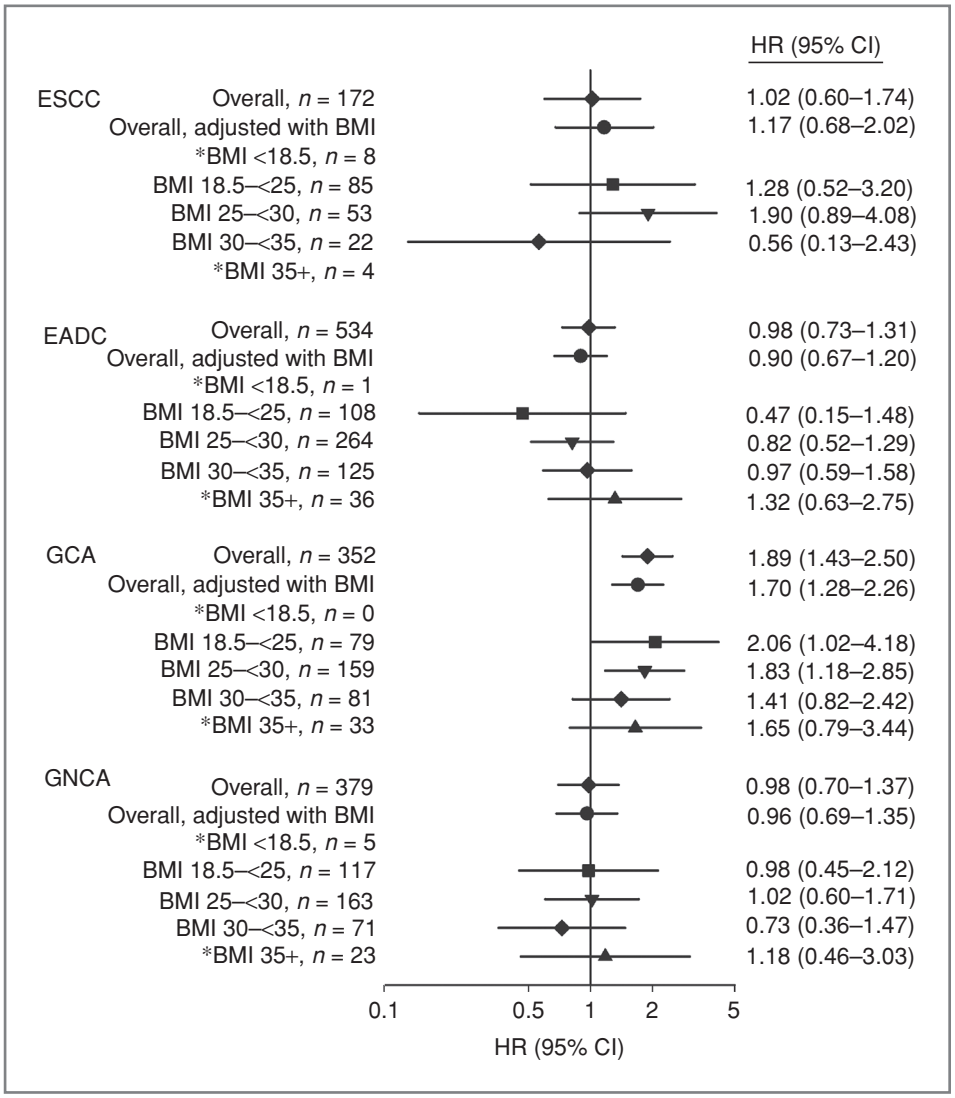

Figure 1. Association between self-reported diabetes and the risk of UGI cancers on adjustment for and stratification by BMI. The overall risk estimates from the cohort in comparison to risk estimates calculated on adjustment with BMI and stratification by WHO-defined BMI categories. Potential confounders included in all models were age, sex, caloric intake, alcohol consumption, smoking status, fruit and vegetable intake, ethnicity, education, and 2 physical activity variables. Models that adjusted for BMI included the categorical BMI variable. We found no evidence for effect modification by BMI: for ESCC, $P_{interaction} = 0.56$; EADC, $P_{interaction} = 0.89$; GCA, $P_{interaction} = 0.83$; GNCA, $P_{interaction} = 0.53$.
*Because of instability, we do not provide estimates for BMI categories with <10 UGI cases per category.

development of cancers of the gastroesophageal junction, but we did not have information on GERD or the use of antireflux therapies in these subjects. We did, however, have information on the use of antacids for a subset of the cohort, and in a subanalysis, we observed similar results on adding antacid use as a potential confounder. Similarly, the addition of aspirin and nonsteroidal anti-inflammatory drug (NSAID) use did not alter the results. We also explored the effect of smoking duration on the risk estimates and found that its addition in the models did not alter our results.

To our knowledge, this is the largest prospective study of the association between diabetes and UGI cancers with information on important confounders, such as smoking and physical activity. We found no association between self-reported diabetes and risk of EADC, ESCC, or GNCA. However, we did find a significant association between self-reported diabetes and an increased risk of GCA. Our results suggest that the metabolic and hormonal changes related to diabetes may play a role in the etiology of GCA independently from BMI.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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