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Diabetes and Risk of Esophageal and Gastric Adenocarcinomas

Xuejuan Jiang, Ph.D.¹, Leslie Bernstein, Ph.D.², Chiu-Chen Tseng, M.S.¹, and Anna H. Wu, Ph.D.¹

¹Department of Preventive Medicine, Keck School of Medicine, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA

²Department of Population Sciences, Beckman Research Institute and City of Hope Comprehensive Cancer Center, Duarte, CA

Abstract

Diabetes has been consistently associated with an increased risk of liver, pancreas and endometrial cancer and has been implicated as a risk factor for esophageal and gastric cancers, although this association has been less well studied. We sought to determine the role of diabetes in the etiology of esophageal, gastric cardia and distal gastric adenocarcinomas. This analysis included patients with esophageal adenocarcinoma (n=209), gastric cardia adenocarcinoma (n=257) and distal gastric adenocarcinoma (n=382), and 1,309 control participants from a population-based case-control study conducted in Los Angeles County. The study included non-Hispanic whites, African Americans, Hispanics and Asian Americans. The association of diabetes with the three tumor types was estimated using polychotomous logistic regression. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated. Nine percent of control participants and 13% of the case patients reported a history of diabetes. After adjustment for age, gender, race, birthplace, education, cigarette smoking status and body mass index, diabetes was associated with an increased risk of esophageal adenocarcinoma (OR, 1.48; 95% CI, 0.94–2.32; P=0.089) and distal gastric adenocarcinoma (OR, 1.47; 95% CI, 1.01–2.15; P=0.045), but was not associated with risk of gastric cardia adenocarcinoma (OR, 0.96; 95% CI, 0.59–1.55; P=0.87). However, the association between diabetes and risk of DGA was statistically significant only among patients for whom we interviewed their next-of-kin. This study further investigated the association between diabetes and adenocarcinomas of the esophagus and distal stomach.

Keywords

diabetes; esophageal adenocarcinoma; gastric adenocarcinoma; case-control study; polychotomous logistic regression

Introduction

The prevalence of diabetes has been increasing globally; rates in North America are among the highest¹. In 2010, 25.6 million or 11.3% of Americans ages 20 years or older had diabetes², with an estimated 1.9 million new cases diagnosed each year. Diabetes has been consistently associated with an increased risk of cancers of the liver, pancreas and endometrium³; however, for many other cancers, data are limited. Over 18 studies have investigated the risk of esophageal and gastric cancer in relation to history of diabetes^{4–22}.

Corresponding author: Anna H. Wu. University of Southern California/Norris Comprehensive Cancer Center, 1441 Eastlake Avenue, Los Angeles, CA 90089-9175, USA. Fax: 1011-1-323-865-0139. annawu@usc.edu.

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However, to our knowledge, only five studies distinguished adenocarcinomas from squamous carcinoma of the esophagus^{17–20, 23} and only two studies^{18, 23} specifically evaluated risk patterns of gastric cardia cancer. In this report, we have investigated whether diabetes is associated with risk of esophageal and gastric adenocarcinoma using data from a large population-based case-control study conducted among residents of Los Angeles County²⁴.

The association between diabetes and cancer risk may be mediated via direct effects of hyperglycemia, insulin resistance and hyperinsulinemia³ or indirectly via risk factors common to both diabetes and cancer, such as obesity, diet and tobacco smoking. In the Los Angeles case-control study, cigarette smoking²⁴, body size²⁴, history of reflux²⁵ and fiber intake²⁶ have been significantly associated with esophageal and gastric adenocarcinoma. Thus, we have also explored whether the association between diabetes and risk of esophageal and gastric adenocarcinoma is modified by age, body mass index, fiber intake, reflux symptoms and cigarette smoking.

Material and Methods

Study Population

The details of the study population and design have been described previously^{24–32}. Briefly, cases for this study were men and women, ages 30–74 years with histologically confirmed, incident esophageal adenocarcinoma (EA; International Classification of Disease for Oncology code C15.0–C15.9), gastric cardiac adenocarcinoma (GCA; International Classification of Disease for Oncology code C16.0), or distal gastric adenocarcinoma (DGA; International Classification of Disease for Oncology codes C16.1–C16.6 and C16.8–C16.9) diagnosed between 1992 and 1997. They were identified by the Los Angeles County Cancer Surveillance Program, the population-based cancer registry covering Los Angeles County, a member of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, and the statewide California Cancer Registry. Control participants were subjects without a diagnosis of gastric or esophageal cancer. They were individually matched to each case patient on sex, race, age (± 5 years) and neighborhood of residence. A systematic algorithm based on the address of the case patient was used to recruit control subjects²⁵. To increase the study's statistical power, we sought two control participants for each case patient whenever possible.

In-person interviews were conducted with participants. Next-of-kin (NOK) were interviewed when case patients were unable to be interviewed due to death or illness. Although it was not feasible to blind interviewers to case (or NOK) or control status, interviewers and study participants were not aware of the study hypotheses. Written informed consent was obtained from each study participant before interview. A total of 947 case patients were interviewed, representing 77% of the 1230 eligible patients who were approached (77% for EA, 74% for GA, and 78% for DGA). Among them, 528 were matched to one control participants and 382 to two or more control participants; 37 had no eligible control participants identified. NOK interviews accounted for 271 (66 EA, 85 GCA and 120 DGA) of the interviews with case patients. We excluded 99 case patients and 47 control subjects because of extreme caloric intake or missing data on diabetes or BMI. A total of 848 case patients (209 with EA, 257 with GCA and 382 with DGA) and 1,309 control participants were included in the current analyses.

Data collection

Cases and their matching controls were interviewed by the same interviewer in almost all instances. A reference date was defined as one year before the date of diagnosis of the case

patient; this same reference date was used for each case patient's matched control subject(s). A structured questionnaire designed specifically for this study was administered during the in-person interview, obtaining data up to the reference date. The interview queried demographic information, smoking history, lifetime use of all types of alcoholic beverages, usual diet, weight at ages 20 and 40 years and on the reference date (referred to as current weight), and height. In addition, we asked detailed questions regarding personal history of conditions of esophagus and gastrointestinal tract and other medical conditions. Specifically, participants were asked if they had diabetes diagnosed by a doctor before the reference date. If the response was yes, participants were then asked age at first diagnosis, treatment received and duration of treatment.

Statistical Analysis

Odds ratios (OR) and corresponding 95% confidence intervals (CI) were estimated. To maximize statistical power, we report results from unconditional polytomous logistic regression with adjustment for the matching variables²⁶ including age (49, 50–59, 60–69, 70 years), sex (male/female) and race (non-Hispanic white, African American, Hispanic, Asian). Birth place (US born, non-US born), level of education (<high school, high school, some college, college graduate or higher), cigarette smoking status (never smoker, former smoker, current smoker) and body mass index (BMI) at reference age (in quartiles) were also included as covariates in the analyses. Results remained materially unchanged if we further adjusted for the duration and intensity of cigarette smoking. We previously showed²⁶ that this approach provided more precise estimates of the ORs while the magnitude of the estimated ORs was consistent with those obtained in separate conditional logistic regression analyses that preserved the original case-control match within each cancer site. Similar results were also observed when we evaluated the effect of diabetes.

One degree of freedom likelihood ratio test was used to assess the homogeneity of diabetes' effect by potential effect modifiers including age, BMI, fiber intake, reflux history, cigarette smoking status and respondent type. We conducted these analyses separately for each type of cancer using unconditional logistic regression.

To perform a meta-analysis^{33, 34} of the studies that examined EA specifically, we identified studies by a computerized search in MEDLINE (January 1960 to June 2011) of all English language and human subject articles. The reference lists of the relevant publications were also reviewed to identify additional studies. Study-specific adjusted estimates of relative risk were obtained from the original study publications and pooled according to the DerSimonian and Laird random effects model³⁵ to allow for variation in true associations across studies. Forest plot was prepared using the Forest Plot Viewer software version 1.00 (The National Toxicology Program, Research Triangle Park, NC). Between-study heterogeneity was tested by the Cochran's *Q* test³⁶ for statistical significance and quantified by I^2 , which was estimated using the equation:

$$I^2 = \frac{Q - \text{degree of freedom}}{Q} \times 100\%.$$

All reported test significance levels (P values) are two-sided. Meta-analysis was performed using STATA 11 (StataCorp, College Station, Texas) and all other analyses were performed using the SAS 9.2 statistical software (SAS Institute Inc., Cary, NC).

Results

Characteristics of the study participants have been described in details previously^{25, 32}. Diabetes was diagnosed in 9% of control participants and 13% of case patients. As shown in Table 1, the prevalence of diabetes among control participants increased with age (P trend=0.018), BMI (P trend<0.001) and fiber intake (P trend=0.035). Diabetes among controls was more prevalent among Hispanics and African Americans than non-Hispanic whites, although the differences by race were not statistically significant (P=0.25). The prevalence of diabetes also did not differ by sex (P=0.14) or cigarette smoking status (P=0.69).

Diabetes was statistically significantly associated with an increased risk of DGA in a model that adjusted for age, sex, race, smoking status and BMI (OR, 1.47; 95% CI, 1.01–2.15). A similar pattern was observed for EA (OR, 1.48; 95% CI 0.94–2.32), although this finding was only marginally statistically significant (Table 2). No association was observed between diabetes and GCA. We also investigated the time interval between the diagnosis of diabetes and the diagnosis of the patient's cancer (for control participants, the date of diagnosis of their matched case was used). Diabetes that had been diagnosed less than 10 years before these dates was associated with an elevated risk for all three tumor types; this finding was statistically significant for DGA (P=0.028). Diabetes that had been diagnosed more than 10 years before these dates was not associated with an increased risk of any tumor type.

Table 3 presents the stratified analyses of diabetes's effect by age, BMI, fiber intake, reflux symptoms, cigarette smoking and respondent type. The diabetes-EA or diabetes-DGA association was more pronounced among older participants, NOK respondents, those with a low BMI (<25 kg/m²), and those without a prior history of reflux but these results were not statistically significantly different. However, the association between diabetes and risk of DGA was statistically significant only among patients for whom we interviewed NOK.

Discussion

Results from this population-based case-control study from Los Angeles County provide further support that diabetes may be associated with an increased the risk of EA and DGA.

A history of diabetes was reported by 9% of our control subjects, a rate comparable with published figures in the US³⁷. Consistent with previous reports^{2, 38}, we also found higher prevalence rates of diabetes among control participants who were Hispanic or African American and those with higher BMI, lending further support to the reliability of our exposure assessment by self-report. The observation of a higher level of fiber intake among diabetic control participants is not surprising since these individuals may have changed their dietary habits to improve glucose tolerance after the diagnosis of diabetes.

Four case-control studies^{17–20} and one prospective cohort study²³ have investigated the diabetes-EA association (Supplemental Table 1). Three of the five studies showed a positive association; this included females in England and Scotland¹⁷ (OR, 7.00; 95% CI, 0.86–56.89), veterans in Portland, US²⁰ (OR, 2.78; 95% CI, 1.38–5.62), and men and women in Australia¹⁸ (OR, 1.32; 95% CI, 0.85–2.05). No association was found in the NIH-AARP Diet and Health study (HR, 0.90; 95% CI, 0.67–1.20)²³. Similarly, no association was found when distal EA was examined in combination with GCA among 10,465 veterans with GERD identified within the US Veterans Affairs National Patient Care Datasets (OR, 1.1; 95% CI, 0.8–1.5)¹⁹. Limitations of these studies include small sample sizes^{17, 20}, non-population-based^{19, 20}, use of medical records for exposure assessment^{19, 20} and lack of information on the duration of diabetes^{17, 19, 20, 23}. A random-effects meta-analysis^{33, 34} of the four prior studies^{17, 18, 20, 23} that examined EA specifically as well as our result on EA

risk produced a combined OR of 1.48 (95% CI, 0.96–2.28; $P = 0.077$; test for heterogeneity: $P = 0.011$, $I^2 = 69\%$). Supplemental Figure 1 shows the forest plot for this meta-analysis.

Although over 13 studies^{4–16, 22} have investigated the association between gastric cancer and diabetes, only few^{18, 19, 23} have evaluated this by gastric cancer subtype (Supplemental Table 1). Rubenstein et al.¹⁹ examined GCA in combination with distal EA and did not find any evidence of an association with diabetes. Neale et al.¹⁸ observed that individuals with GCA were more likely than controls to report a history of diabetes and the association was stronger for diabetes that had been diagnosed >10 years (OR, 2.16; 95% CI, 1.16–4.04). Using data from the NIH-AARP Diet and Health study, Lin et al.²³ recently reported a significant association between diabetes and risk of GCA, but no significant association of diabetes with risk of gastric noncardia adenocarcinoma. Contrary to Lin et al., in the present study, we did not find any association between GCA and diabetes; however, an increased risk of DGA was observed among those with diabetes. The inconsistency observed among the current limited data highlights the need for additional research on diabetes, including information on age at diagnosis and treatment for diabetes.

Several mechanisms have been proposed to explain associations between diabetes and cancer. Metabolic abnormalities associated with diabetes, such as insulin resistance, compensatory hyperinsulinemia, the elevated levels of bioactive insulin-like growth factor and/or chronic inflammation, can stimulate cancer cell mitogenesis, proliferation, invasion and metastasis, therefore enhance the promotion and progression of cancer cells³. Hyperinsulinemia has been shown to increase bioavailable estrogen and testosterone³⁹, sex hormones which have been suggested to play a role in the development of EA and GCA⁴⁰. In addition, early evidence suggests that some diabetes treatments may also affect cancer risk³. Specific to the esophagus and stomach, it has also been reported that diabetic patients frequently suffer from delayed gastric emptying⁴¹, which has been associated with an increased risk of reflux symptoms⁴², a known risk factor for esophageal cancer in the current and previous studies²⁵. In our study, the diabetes-EA/DGA associations were more pronounced among participants without a prior history of reflux, suggesting that delayed gastric emptying is unlikely to explain our observation. It is also possible that the associations between diabetes and cancer are not causal, instead may be due to shared common risk factors such as aging and obesity. We controlled for a number of known risk factors including age, BMI and cigarette smoking in our analyses; further, the associations we observed between diabetes and EA and GCA did not differ by age and appeared to be more pronounced among subjects with low BMI (<25). Therefore, it is unlikely that the effect of diabetes was mediated by these shared risk factors.

Our study represents one of the few large population-based studies that have investigated the role of diabetes in the etiology of adenocarcinoma of the esophagus and stomach. However, our study has a number of limitations that warrant consideration in interpreting the results. Information on diabetes were based on self-report, although we considered only physician-diagnosed disease and asked extensive questions regarding diabetes (e.g. age at diagnosis, treatment). Another limitation is the relatively small number of individuals with diabetes, particularly in the subgroup analyses, increasing the likelihood of spurious associations. Despite the significant association between diabetes and DGA, our analysis did not reveal a trend toward increasing cancer risk among individuals with longer duration of diabetes. Also, our observed association between diabetes and DGA was more pronounced when restricted to patients for whom we interviewed their NOK. This may be because these patients were more susceptible to diabetes-induced complications. As individuals with diabetes are at a higher risk of cardiovascular diseases and mortality⁴³, these susceptible individuals were also more likely to be ill or deceased and consequently participate in the study through next-of-kin interviews. This was supported by the higher rate of next-of-kin

interview among diabetic cases (41%) than that among non-diabetic cases (26%) in our study.

In summary, our data suggest that diabetes may be associated with an increased risk of EA and DGA. Future studies with larger sample sizes are needed to confirm our findings, further examine timing of diabetes (age at diagnosis of diabetes, interval between age at diagnosis of diabetes and cancer), and explore possible mechanisms by which diabetes may increase the risk of these tumor types.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index
CI	confidence interval
DGA	distal gastric adenocarcinoma
EA	esophageal adenocarcinoma
GCA	gastric cardia adenocarcinoma
NOK	next of kin
OR	odds ratio
SEER	Surveillance, Epidemiology, and End Results program

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Novelty and impact

This population-based study further examined the relationship between diabetes and adenocarcinoma of the esophagus and stomach. This investigation represents one of the few studies that distinguished adenocarcinoma from squamous carcinoma of the esophagus and specifically evaluated risk patterns of gastric cardia cancer.

Table 1

Prevalence of diabetes by demographic and lifestyle characteristics among control subjects

N (row percent)	Diabetes		<i>P</i> ¹
	No	Yes	
Age			
49	262 (95%)	15 (5%)	<i>0.018</i>
50–59	305 (92%)	28 (8%)	
60–69	409 (91%)	41 (9%)	
70	221 (89%)	28 (11%)	
Sex			
Male	883 (91%)	90 (9%)	<i>0.14</i>
Female	314 (93%)	22 (7%)	
Race			
Non-Hispanic white	761 (92%)	64 (8%)	<i>0.25</i>
African American	75 (86%)	12 (14%)	
Hispanics	257 (90%)	27 (10%)	
Asian American	104 (92%)	9 (8%)	
BMI ²			
Q1	365 (96%)	15 (4%)	<i><0.001</i>
Q2	307 (93%)	24 (7%)	
Q3	269 (89%)	32 (11%)	
Q4	256 (86%)	41 (14%)	
Fiber intake density ³			
Q1	306 (93%)	24 (7%)	<i>0.035</i>
Q2	309 (94%)	19 (6%)	
Q3	292 (89%)	35 (11%)	
Q4	290 (90%)	34 (10%)	
Reflux symptoms			
No	1036 (92%)	91 (8%)	<i>0.15</i>
Yes	161 (88%)	21 (12%)	
Cigarette smoking status			
Never smokers	479 (92%)	39 (8%)	<i>0.69</i>
Former smokers	518 (90%)	57 (10%)	
Current smokers	200 (63%)	16 (7%)	

Abbreviations: BMI, body mass index.

¹ χ^2 test for race and Mantel-Haenszel χ^2 test for other variables.²Quartile cut points for current BMI are 23, >23–25, >25–28, >28 in males, and 22, >22–25, >25–28.25, >28.25 in females.³Quartile cut points for total fiber intake are 8.9, >8.9–11, >11–14.5, >14.5 gm/day in males, and are 10.9, >10.9–13, >13–16.7, >16.7 gm/day in females.

Table 2
Adjusted odds ratios (and 95% confidence intervals) for esophageal and gastric adenocarcinoma in relation to diabetes.

	Controls	EA			GCA			DGA		
		Cases	OR (95% CI) ^I	P ^I	Cases	OR (95% CI) ^I	P ^I	Cases	OR (95% CI) ^I	P ^I
No diabetes	1197	178	1.00 (ref)		233	1.00 (ref)		327	1.00 (ref)	
Diabetes	112	31	1.48 (0.94–2.32)	0.089	24	0.96 (0.59–1.55)	0.87	55	1.47 (1.01–2.15)	0.045
Duration of diabetes										
2 years	17	6	1.69 (0.62–4.55)	0.30	6	1.42 (0.54–3.77)	0.48	9	1.78 (0.74–4.30)	0.20
>2–10 yrs	37	13	1.82 (0.92–3.61)	0.084	12	1.42 (0.71–2.82)	0.32	25	1.89 (1.07–3.34)	0.028
>10 yrs	58	12	1.19 (0.61–2.33)	0.61	6	0.50 (0.21–1.18)	0.12	21	1.11 (0.63–1.94)	0.72

Abbreviations: EA, esophageal adenocarcinoma; GCA, gastric cardia adenocarcinoma; DGA, distal gastric adenocarcinoma; OR, odds ratio; CI, confidence interval; NOK, next of kin.

^IResults were estimated from multivariate unconditional polytomous logistic regression, with adjustment for age, sex, race, education, birth place, cigarette smoking status and body mass index.

Table 3

Adjusted odds ratios (and 95% confidence intervals) for esophageal and gastric adenocarcinoma in relation to diabetes by subgroups of interest. Numbers of cases and controls shown are those with a positive history of diabetes.

Subgroup	EA			GCA			DGA			
	Controls	Cases	OR (95% CI) ¹	P ¹	Cases	OR (95% CI) ¹	P ¹	Cases	OR (95% CI) ¹	P ¹
Age 60	45	14	1.38 (0.74–2.56)	0.31	9	1.04 (0.55–1.93)	0.91	16	1.41 (0.83–2.39)	0.20
Age >60	67	17	1.54 (0.93–2.56)	0.094	15	0.91 (0.53–1.58)	0.75	39	1.51 (0.98–2.32)	0.061
<i>P</i> _{heterogeneity}			0.30			0.85			0.48	
BMI 25	39	13	2.62 (1.30–5.27)	0.007	8	1.04 (0.47–2.32)	0.92	24	1.72 (0.97–3.07)	0.065
BMI >25	73	18	1.05 (0.59–1.89)	0.87	16	0.91 (0.50–1.65)	0.74	31	1.32 (0.80–2.17)	0.28
<i>P</i> _{heterogeneity}			0.058			0.78			0.71	
Fiber intake median ²	43	16	1.30 (0.69–2.47)	0.42	15	1.14 (0.60–2.17)	0.68	25	1.59 (0.89–2.81)	0.11
Fiber intake > median ²	69	15	1.99 (1.04–3.81)	0.037	9	0.83 (0.39–1.74)	0.61	30	1.42 (0.86–2.35)	0.17
<i>P</i> _{heterogeneity}			0.19			0.54			0.78	
Negative reflux history	91	18	1.55 (0.88–2.75)	0.13	15	0.87 (0.48–1.56)	0.64	46	1.56 (1.03–2.36)	0.036
Positive reflux history	21	13	1.04 (0.48–2.25)	0.93	9	0.96 (0.41–2.25)	0.92	9	1.04 (0.41–2.63)	0.94
<i>P</i> _{heterogeneity}			0.52			0.90			0.49	
Never smokers	39	7	1.88 (0.77–4.59)	0.17	6	1.03 (0.41–2.57)	0.95	19	1.39 (0.73–2.65)	0.32
Smokers	73	24	1.38 (0.82–2.32)	0.22	18	0.93 (0.53–1.63)	0.81	36	1.51 (0.95–2.40)	0.081
<i>P</i> _{heterogeneity}			0.64			0.84			0.85	
Self-respondent cancer participants	112	19	1.17 (0.67–2.02)	0.58	16	0.88 (0.50–1.56)	0.67	30	1.03 (0.65–1.63)	0.91
NOK respondents for cancer patients	112	12	2.29 (1.14–4.60)	0.019	8	1.13 (0.52–2.48)	0.76	25	3.37 (1.96–5.79)	<0.001
<i>P</i> _{heterogeneity}			0.35			0.90			0.0007	

Abbreviations: EA, esophageal adenocarcinoma; GCA, gastric cardia adenocarcinoma; DGA, distal gastric adenocarcinoma; OR, odds ratio; CI, confidence interval; NOK, next of kin; BMI, body mass index.

¹ Results were estimated from multivariate unconditional polytomous logistic regression, with adjustment for age, sex, race, education, birth place, cigarette smoking status and BMI.

² Median for total fiber intake is 11 gm/day in males and 13 gm/day in females.