

FAMILY HISTORY OF CANCER AND RISK OF ESOPHAGEAL AND GASTRIC CANCERS IN THE UNITED STATES

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The worldwide rates for histology- and subsite-specific types of esophageal and gastric cancer reveal strikingly divergent patterns. The contribution of environmental and genetic factors has been explored in several high-incidence areas, but data on genetic influences are scarce for Western countries. Using data from a multicenter, population-based, case-control study on 1,143 cases and 695 controls in the United States, we evaluated whether a family history of digestive or other cancers was associated with an increased risk of esophageal adenocarcinoma (n = 293), esophageal squamous cell carcinoma (n = 221), gastric cardia adenocarcinoma (n = 261) or non-cardia gastric adenocarcinoma (n = 368). After adjusting for other risk factors, individuals reporting a family history of digestive cancers experienced no increased risk of either type of esophageal cancer but they were prone to adenocarcinomas of the gastric cardia [odds ratio (OR) = 1.34, 95% confidence interval (CI) 0.91–1.97] and non-cardia segments (OR = 1.46, 95% CI 1.03–2.08). This familial tendency, particularly for non-cardia gastric tumors, was largely explained by an association with family history of stomach cancer (OR = 2.52, 95% CI 1.50–4.23). In addition, family history of breast cancer was associated with increased risks of esophageal adenocarcinoma (OR = 1.74, 95% CI 1.07–2.83) and non-cardia gastric adenocarcinoma (OR = 1.76, 95% CI 1.09–2.82). Also seen were non-significant familial associations of esophageal squamous-cell cancer with prostate cancer as well as non-cardia gastric cancer with leukemia and brain tumors, though these relationships must be interpreted with caution. Our data point to the role of familial susceptibility to gastric cancer, but not to any form of esophageal cancer, in the United States.

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Key words: esophageal neoplasm; stomach neoplasm; case-control study; family history; United States

Incidence rates for adenocarcinomas of the esophagus and gastric cardia have risen steeply in industrialized countries since the 1970s, while rates for esophageal squamous cell carcinoma and non-cardia gastric adenocarcinoma have remained stable or decreased.^{1,2} Both the rapidity of these changes and the striking geographic variation of these tumors suggest that environmental factors play a major etiologic role.^{3–9} However, genetic or other endogenous factors may also influence susceptibility to these tumors. Numerous studies from populations in China, Iran, Italy, Japan and Poland have reported familial aggregation of esophageal and gastric cancers.^{10–17} In Western countries, very few epidemiologic studies have evaluated the familial risk of type-specific esophageal cancer or subsite-specific gastric cancer.^{18–20} We conducted this analysis to determine whether a family history of digestive or other cancers is associated with an increased risk of esophageal adenocarcinoma, esophageal squamous cell carcinoma, gastric cardia adenocarcinoma or non-cardia gastric adenocarci-

noma. Data were collected as part of a large multicenter, population-based, case-control study of the 4 tumor types.

MATERIAL AND METHODS

Study methods have been described in detail elsewhere.⁵ Briefly, individuals aged 30 to 79 years and diagnosed during the period 1993–1995 with primary invasive cancer of the esophagus or stomach were identified through rapid-reporting systems in 3 areas with population-based registries: the state of Connecticut, a 15-county area of New Jersey and a 3-county area of northwestern Washington state. All individuals diagnosed with adenocarcinoma of the esophagus or gastric cardia (target cases) were eligible. Those diagnosed with squamous cell carcinoma of the esophagus or adenocarcinoma elsewhere in the stomach (comparison cases) were frequency-matched to the expected distribution of target cases on the basis of geographic area and 5-year age group in Connecticut, New Jersey and Washington; on the basis of sex in New Jersey and Washington; and on the basis of race (white or other) in New Jersey. Study pathologists reviewed endoscopic, surgical and pathologic data on >99% of cases to determine the histologic type and specific site of origin of tumors. Population-based control subjects were selected by random-digit dialing for those aged 30 to 64 years and through random sampling of Health Care Financing Administration (HCFA) rosters for controls aged 65 to 79 years. Controls were frequency-matched to the expected distribution of target cases on the basis of 5-year age group and sex.

We obtained interview data for 77.1% of eligible cases and 70.2% of eligible controls. Interviews were conducted with the next closest relative (usually the spouse) rather than the study subject for 31.1% of cases and 3.5% of controls.

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In-person, structured interviews were used to collect information on family history of cancer and other risk factors, including demographic characteristics, medical history, smoking, alcohol consumption, medication use, diet and occupation. Subjects were asked to report whether any parents, siblings or children had been diagnosed with a cancer, including hematopoietic cancers such as leukemia, lymphoma and multiple myeloma. If subjects answered affirmatively, they reported which relative(s) had a cancer diagnosis, the type(s) of cancer and the age(s) at diagnosis. All subjects provided information on the number of full brothers and sisters and children (not including adopted children or stepchildren) living or deceased. Subjects who reported a family history of cancer at a particular site (defined by 1 or more relatives with the site-specific cancer) were classified as exposed. Family history of digestive cancers, including the esophagus (ICD-9^{20a} code 150), stomach (ICD-9 151), colon/rectum (ICD-9 153–154), other digestive organs (ICD-9 152, 155–159) and non-digestive cancers were examined separately. Non-digestive cancers considered in the analysis included cancers of the respiratory system (ICD-9 160–165), female breast (ICD-9 174), brain (ICD-9 191) and prostate (ICD-9 185), as well as leukemia (ICD-9 208) and cancers of unknown site (ICD-9 199). These cancer types were reported by enough subjects to provide sufficient data for analysis. In analyses of digestive cancers, unexposed subjects were those who did not report a family history of any digestive cancers. In analyses of non-digestive cancers, unexposed subjects were those who did not report a family history of cancer at those sites.

Unconditional logistic regression was used to calculate odds ratios (ORs), as an estimate of the relative risk, and corresponding 95% confidence intervals (CIs) for each type of cancer among subjects reporting a family history of cancer compared to those without a family history. We also assessed whether cases and controls differed with respect to the number of first-degree relatives with cancer (0, 1 or more than 1). We conducted subanalyses on cases with an early age at onset, to determine if the risk associated with a family history of cancer was greater at younger ages. Age cut-offs for early-onset tumors were defined separately for each form of cancer, based on the age distribution of cancer incidence data from the Surveillance, Epidemiology and End Results (SEER) program. Type-specific diagnoses at or before ages corresponding to the 25th percentile were considered early-onset cases. We also assessed the risk of each cancer type among subjects who reported 1 or more relative with an early-onset diagnosis of cancer compared to those who did not.

All models included as covariates study center, age, smoking (5 categories, including never-smokers and quartiles of pack-years, with cut points from distributions of male and female controls) and respondent type (study subject or proxy). Additional adjustment for the following characteristics was included in site-specific analyses as noted in the tables: race (white, black, other), body mass index (BMI; quartiles based on usual adult weight and height, with cut points from gender-specific control distributions), gender, household income (<\$15,000, \$15,000–\$29,999, \$30,000–\$49,999, \$50,000–\$74,999 or >\$75,000) and alcohol use (none, ≤7, >7 but ≤14, >14 but ≤42, >42 drinks/week). Education, family size and dietary intake of sodium and nitrites did not confound our results. In determining the final models, we evaluated potential predictors and confounders for each case group separately. As a result, the final models include covariates that differ according to case type.

RESULTS

Demographic and other characteristics of each of the 4 case groups and controls have been described in detail elsewhere.^{5,21} These data are summarized in Table I. Among controls, subjects reporting a family history of digestive cancers tended to be older, female and current smokers and to have a slightly higher BMI than those not reporting a family history of those cancers (data not shown). The sections that follow present the associations between history of cancer and risk of each tumor type separately.

Esophageal adenocarcinoma

The risk of esophageal adenocarcinoma was not associated with a family history of digestive cancers, either as a group or by individual site (OR = 0.96, 95% CI 0.64–1.45) (Table II). Over 90% (269/293) of these cases had tumors located in the lowest third of the esophagus; analyses restricted to this subgroup yielded no difference in results. No relationships emerged when the analysis was restricted to early-onset cases, *i.e.*, those in the youngest quartile (≤58 years) of age at diagnosis (OR = 1.18, 95% CI 0.49–2.87).

However, a significant 74% increase in risk was associated with a family history of breast cancer (Table III). Estimates were similar whether the affected relative was a mother (OR = 1.70, 95% CI 0.91–3.17) or a sister (OR = 2.13, 95% CI 0.98–4.63) and rose to 2.31 (95% CI 1.11–4.82) if the relative was diagnosed with breast cancer before the age of 50 years. Cases were no more likely than controls to report a family history of any other form of cancer.

Esophageal squamous cell carcinoma

The risk of esophageal squamous cell carcinoma was unrelated to a family history of any form of digestive cancer (Table II), even when analyses focused on early-onset cases. The distribution of these cases by location yielded 19% (41/221) in the upper third, 43% (96/221) in the middle third and 33% (72/221) in the lower third of the esophagus. Stratification by tumor location yielded no associations, and small numbers were present in each stratum. An increased, marginally non-significant risk was associated with a family history of prostate cancer (OR = 2.12, 95% CI 0.93–4.81). Estimates did not materially differ whether the affected relative was a father (OR = 1.90, 95% CI 0.57–6.33) or a brother (OR = 2.44, 95% CI 0.82–7.31). No excess risks were related to a family history of other tumors (Table III).

Gastric cardia adenocarcinoma

The risk of gastric cardia adenocarcinoma was non-significantly increased (OR = 1.34, 95% CI 0.91–1.97) among subjects with a family history of digestive cancers and rose further (OR = 1.91, 95% CI 0.83–4.40) when analyses focused on early-onset cases (Table II). ORs ranged from 1.07 for a family history of esophageal cancer (95% CI 0.33–3.46) to 1.53 for a family history of stomach cancer (95% CI 0.81–2.90). Risk was increased 4-fold among individuals who reported esophageal cancer in a sibling (OR = 4.28, 95% CI 0.84–21.83) but was decreased among those reporting esophageal cancer in a parent (OR = 0.19, 95% CI 0.02–1.89). Risk was not increased in those with a family history of other cancers (Table III).

Non-cardia gastric adenocarcinoma

The risk of non-cardia gastric adenocarcinoma was increased in association with a family history of digestive cancers (OR = 1.46, 95% CI 1.03–2.08). This relationship was due to a familial tendency to gastric cancer (OR = 2.52, 95% CI 1.50–4.23) (Table II). Additional adjustment for dietary sodium and nitrite intake did not materially change these results (data not shown). Risk was most pronounced in subjects reporting 2 or more family members with gastric cancer (OR = 12.1, 95% CI 1.35–108.5) but was not further increased among early-onset cases. Risk was unrelated to a family history of other digestive tumors, regardless of age at diagnosis of the case or affected family member.

The risk of non-cardia gastric adenocarcinoma was increased in subjects reporting a family history of breast cancer (OR = 1.76, 95% CI 1.09–2.82) (Table III). The increased risk was limited to subjects reporting breast cancer in a sister (OR = 4.02, 95% CI 2.10–7.68) and did not extend to those with an affected mother (OR = 0.79, 95% CI 0.34–1.82). Risk was increased further if the sister was diagnosed before the age of 50 years (OR = 6.11, 95% CI 2.03–18.41).

In addition, risks were increased in subjects reporting a family history of cancer of unknown origin (OR = 2.44, 95% CI 1.32–4.49) and to a non-significant level in those reporting a family history of leukemia or brain tumors (Table III).

TABLE I—SELECTED CHARACTERISTICS OF CASES AND CONTROLS

	Controls (n = 695)		Esophageal adenocarcinoma (n = 293)		Esophageal squamous cell carcinoma (n = 221)		Gastric cardia adenocarcinoma (n = 261)		Non-cardia gastric adenocarcinoma (n = 368)	
	N	%	N	%	N	%	N	%	N	%
Sex										
Male	555	79.9	245	83.6	176	79.6	223	85.4	254	69.0
Female	140	20.1	48	16.4	45	20.4	38	14.6	114	31.0
Race										
White	646	93	289	98.6	168	76	252	96.6	306	83.2
Black	34	4.9	2.0	0.7	48	21.8	4	1.5	36	9.8
Native American/Asian/Other	15	2.2	2	0.7	5	2.3	5	1.9	26	7.1
Age (years)										
≤35–45	67	9.7	23	7.9	10	3.6	26	10.1	21	6.5
46–55	112	16.1	47	16.0	24	10.8	38	14.6	43	11.7
56–65	217	31.2	71	24.2	69	31.2	75	28.8	81	22.0
66–75	244	35.1	115	39.2	92	41.6	102	39.1	171	46.5
76–80	55	7.9	37	12.6	26	11.8	20	7.7	52	14.1
Household income										
≤\$29,999	270	38.9	147	50.2	146	66.0	122	46.7	202	54.5
\$30,000–\$74,999	301	43.3	111	37.8	65	29.4	102	39.1	146	39.7
≥\$75,000	124	17.8	35	12.0	10	4.5	37	14.2	20	5.8
Quartile of BMI (usual)										
1 (lowest)	172	24.8	45	15.4	79	35.8	54	20.7	105	28.5
2	173	24.9	63	21.5	50	22.6	51	19.5	77	22.9
3	174	25.0	85	29.0	53	24.0	70	26.8	91	24.7
4 (highest)	173	24.9	99	33.8	38	17.2	86	33.0	92	25.0
Alcohol consumption										
≤14 drinks/week	510	73.4	192	65.5	62	28.1	177	67.9	257	75.2
>14 drinks/week	178	25.6	87	29.7	141	63.8	76	29.2	75	20.4
Cigarette smoking										
Never	215	30.9	58	19.8	20	9.1	45	17.2	95	25.8
Former	296	42.6	144	49.2	91	41.2	123	47.1	164	44.6
Current	154	22.2	83	28.3	105	47.5	83	31.8	94	25.5
Mean family size (includes parents, siblings and children)	5.0 (SD = 2.6)		4.9 (SD = 2.3)		5.7 (SD = 3.5)		5.2 (SD = 2.5)		6.3 (SD = 2.6)	
Family history of cancer										
Yes	354	50.9	146	49.8	105	47.5	148	56.7	211	57.3
Digestive only	75	10.8	34	11.6	25	11.3	32	12.3	48	13.0
Non-digestive only	232	33.4	94	32.1	67	30.3	89	34.1	119	32.3
Both	47	6.8	18	6.1	13	5.9	27	10.3	44	12.0
No	331	47.6	134	45.7	108	48.9	108	41.4	149	40.5
Missing/unknown	10	1.4	13	4.4	8	3.6	5	1.9	8	2.2

TABLE II—ASSOCIATION BETWEEN FAMILY HISTORY OF DIGESTIVE CANCER AND RISK OF ESOPHAGEAL AND GASTRIC CANCERS¹

Cancer site (ICD-9 code)	Controls	Esophageal Adenocarcinoma			Esophageal Squamous Cell Carcinoma			Gastric Cardia Adenocarcinoma			Non-Cardia Gastric Adenocarcinoma		
		Number	OR ²	95% CI	Number	OR ³	95% CI	Number	OR ⁴	95% CI	Number	OR ⁵	95% CI
Any digestive site (150–159)													
No	573	241	1.00	—	183	1.00	—	202	1.00	—	276	1.00	—
Yes	122	52	0.96	0.64–1.45	38	0.99	0.58–1.68	59	1.34	0.91–1.97	92	1.46	1.03–2.08
Esophagus (150)	11	5	0.88	0.26–3.04	0	(N/A)	—	5	1.07	0.33–3.46	4	0.49	0.12–2.04
Stomach (151)	35	20	1.31	0.68–2.53	13	0.98	0.42–2.27	20	1.53	0.81–2.90	50	2.52	1.50–4.23
Colon/rectum (153–154)	49	15	0.78	0.40–1.50	18	1.36	0.63–2.90	22	1.24	0.70–2.22	24	1.07	0.61–1.90
Other digestive site (152, 155–159)	40	14	0.82	0.41–1.65	10	0.66	0.25–1.73	15	1.21	0.63–2.32	25	1.22	0.68–2.20

¹Numbers of cancers at specific sites exceed total at “any digestive site” because each subject could report multiple cancers. Reference group for all analyses is subjects with no family history of any digestive cancer. ²Adjusted for age at reference date, center, sex, pack-years of smoking, gender-specific quartile of BMI and proxy status. ³Adjusted for age at reference date, center, sex, race, pack-years of smoking, alcohol, income and proxy status. ⁴Adjusted for age at reference date, center, race, pack-years of smoking, gender-specific quartile of BMI and proxy status. ⁵Adjusted for age at reference date, sex, race, pack-years of smoking, gender-specific quartile of BMI, income and proxy status.

DISCUSSION

In our large population-based, case-control study, we observed no association between a family history of any digestive cancer and the risk of either adenocarcinoma or squamous cell carcinoma of the esophagus. In contrast, the risk of gastric cancer was elevated in subjects with a family history of the disease and increased further with the number of affected relatives. Risk of esophageal and non-cardia gastric adenocar-

cinomas was elevated among subjects reporting a family history of breast cancer, while that of esophageal squamous cell carcinoma was non-significantly increased among those with a family history of prostate cancer. Individuals with a family history of leukemia or unspecified type of cancer experienced a 2-fold increased risk of non-cardia gastric adenocarcinoma. For these non-digestive sites, we did not observe further elevations in risk with additional affected relatives.

TABLE III—ASSOCIATION BETWEEN FAMILY HISTORY OF NON-DIGESTIVE CANCER AND RISK OF ESOPHAGEAL AND GASTRIC CANCERS¹

Cancer site (ICD-9 code)	Controls	Esophageal Adenocarcinoma			Esophageal Squamous Cell Carcinoma			Gastric Cardia Adenocarcinoma			Non-Cardia Gastric Adenocarcinoma		
		Number	OR ²	95% CI	Number	OR ³	95% CI	Number	OR ⁴	95% CI	Number	OR ⁵	95% CI
Respiratory system (160–165)													
No	634	271	1.00	—	200	1.00	—	246	1.00	—	343	1.00	—
Yes	61	22	0.84	0.48–1.49	21	0.95	0.47–1.92	15	1.30	0.80–2.10	25	1.31	0.82–2.10
Breast (174–175)													
No	636	254	1.00	—	207	1.00	—	241	1.00	—	329	1.00	—
Yes	58	39	1.74	1.07–2.83	14	0.67	0.30–1.50	20	0.75	0.41–1.35	39	1.76	1.09–2.82
Brain (191)													
No	682	290	1.00	—	219	1.00	—	254	1.00	—	355	1.00	—
Yes	13	3	0.36	0.08–1.70	2	0.56	0.09–3.60	7	1.18	0.39–3.56	13	1.52	0.58–4.01
Prostate (185)													
No	664	283	1.00	—	204	1.00	—	250	1.00	—	356	1.00	—
Yes	31	10	0.66	0.29–1.51	17	2.12	0.93–4.81	11	1.02	0.47–2.19	12	0.75	0.35–1.59
Leukemia (208)													
No	682	287	1.00	—	220	1.00	—	252	1.00	—	351	1.00	—
Yes	13	6	1.06	0.36–3.11	1	0.84	0.10–6.94	9	2.22	0.84–5.85	17	2.08	0.92–4.69
Unknown primary site (199)													
No	672	278	1.00	—	205	1.00	—	243	1.00	—	337	1.00	—
Yes	23	15	1.26	0.60–2.66	16	1.63	0.65–4.11	18	1.33	0.63–2.82	31	2.44	1.32–4.49

¹Reference group in each analysis is subjects with no family history of cancer at that site.—²Adjusted for age at reference date, center, sex, pack-years of smoking, gender-specific quartile of BMI and proxy status.—³Adjusted for age at reference date, center, sex, race, pack-years of smoking, alcohol, income and proxy status.—⁴Adjusted for age at reference date, center, race, pack-years of smoking, gender-specific quartile of BMI and proxy status.—⁵Adjusted for age at reference date, sex, race, pack-years of smoking, gender-specific quartile of BMI, income and proxy status.

Our study is subject to a number of limitations, especially the potential for recall bias since family history data were based on self-reported information from cases and controls. This type of bias may contribute to excess risks seen among subjects reporting a family history of several apparently unrelated cancers. Moreover, self-reported data are subject to greater misclassification of the primary site, which may result in artificially high numbers for cancers of unknown origin or for certain tumors such as the brain, which is a common site of metastasis. However, we found no association between esophageal cancer risk and family history of digestive cancers, even though one might expect some over-reporting of these tumors by cases. Furthermore, family history data were collected for first-degree relatives only, about whom such information is generally more reliable.^{22–25}

While our findings for esophageal cancer are consistent with a similar study conducted in Sweden,¹⁸ they are at odds with reports from high-incidence areas such as China, where individuals reporting a family history of the disease appear to be at sharply increased risk.^{10–13} Squamous cell tumors account for the vast majority of esophageal carcinomas in China but only about half of those diagnosed in the United States, but we found no evidence of a familial tendency for either squamous cell cancer or adenocarcinoma of the esophagus. The discrepancy in findings suggests that in China genetic determinants of squamous cell carcinoma are more prominent and/or environmental exposures, *e.g.*, diet, are more closely shared by family members. Furthermore, the sample size of our study was too small to detect the rare familial occurrences involving esophageal squamous cell carcinoma associated with tylosis (palmoplantar hyperkeratosis) or esophageal adenocarcinoma associated with Barrett's metaplasia.^{26–28}

Studies from various countries, including Italy,^{29,30} Japan,¹⁴ Poland,¹⁷ Sweden¹⁸ and China,^{15,16} have reported a familial tendency to gastric cancer. In our study, familial susceptibility was mainly associated with gastric cancers distal to the cardia, but the modest familial risk observed with gastric cardia tumors suggests that tumors arising in the cardia represent a heterogeneous mixture of lower esophageal and gastric adenocarcinomas. Confounding by usual adult dietary patterns is unlikely to account for these findings as the results were essentially unchanged after adjusting for dietary intake of sodium and ni-

trites; however, early-life exposure to *Helicobacter pylori* may contribute to the familial pattern.^{31–34} Although we were unable to distinguish between the diffuse and intestinal types of gastric cancer in our series, a familial tendency has been reported for both histologic types.¹⁷ The role of genetic susceptibility has been strengthened by the discovery of germline mutations of the E-cadherin gene in families prone to the diffuse type of gastric cancer³⁵ and by the observation that genetic polymorphisms of IL-1 promote development of the intestinal type of gastric cancer associated with *H. pylori* infection.^{33,34}

In our data, individuals with a family history of breast cancer were at increased risk of adenocarcinomas arising in the esophagus and the non-cardia portion of the stomach. In other studies, such individuals have been reported to have a non-significantly increased risk of adenocarcinomas of the cardia¹⁸ and esophagus but not the distal stomach.²⁰ Although our findings may be related to uncontrolled confounding or to multiple comparisons, it is interesting that excess risks of esophageal adenocarcinoma and, to a lesser extent, esophageal squamous cell carcinoma and distal gastric cancer have been reported as a second cancer among women with breast cancer.³⁶ For esophageal cancer, the excess risk after breast cancer appears to be partly due to radiotherapy.³⁷ Also in our study, subjects with a family history of prostate cancer had a non-significantly increased risk of esophageal squamous cell cancer, whereas such individuals were somewhat prone to esophageal²⁰ and gastric adenocarcinomas in previous studies.^{18,20} In addition, we noted familial associations between non-cardia gastric cancer and leukemia as well as brain tumors. Population-based genetic epidemiologic studies relying on the reconstruction of family relationships in cancer incidence data have documented a familial tendency to gastric cancer in Western populations.^{38–40} Such studies have also reported that gastric cancer may have familial associations with cancers of the breast,⁴¹ brain,⁴⁰ pancreas³⁸ and female genital system.⁴⁰ Although these data along with our findings must be interpreted cautiously in view of multiple comparisons, further studies are warranted into possible genetic and hormonal mechanisms that may underlie these familial constellations of tumors.

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