

Short Communication

Heredity and Risk of Cancer of the Esophagus and Gastric Cardia¹

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Abstract

The importance of genetic factors in the etiology of esophageal cancer is uncertain. We addressed the question of heredity in a population-based, nationwide case-control study conducted in Sweden during 1995 through 1997. The study involved 189 patients with esophageal adenocarcinoma, 262 with cardia adenocarcinoma, 167 with esophageal squamous cell carcinoma, and, for comparison, 820 control subjects. Familial occurrence of cancer was explored at face-to-face interviews. Logistic regression, with multivariate adjustment for potential confounders, was used to calculate odds ratios (ORs), which estimated relative risk. Occurrence of esophageal cancer among first-degree relatives did not increase the risk of adenocarcinoma or squamous cell carcinoma of the esophagus. Neither were there any significant associations with familial occurrence of gastric cancer or other gastrointestinal tumors. The risk of cardia adenocarcinoma was moderately increased among persons with first-degree relatives with gastric cancer (OR, 1.6; 95% confidence interval, 1.0–2.6). Familial occurrence of any cancer was not associated with increased risks of any of the three studied tumors. In conclusion, heredity does not seem to contribute importantly to the occurrence of esophageal cancer of any histological type. A weak association between familial gastric cancer and the risk of cardia cancer may represent a genetic link.

Introduction

The incidence of esophageal adenocarcinoma is rising dramatically in Western countries (1). Although genetic factors cannot conceivably explain this increase, such factors may still be of importance, for instance by determining individuals' susceptibility to environmental risk factors. There is a remarkable paucity of data about heredity in cancers of the esophagus and gastroesophageal junction. Published studies are generally small and often lump esophageal squamous cell carcinoma,

esophageal adenocarcinoma, and cardia adenocarcinoma together, and most investigations have been conducted in Asian high-incidence areas, where esophageal cancer may be a disease entity that is different from that in Western populations (2).

Our aim was to gather evidence for or against genetic factors in each of the three main types of cancer of the esophagus and gastroesophageal junction: esophageal squamous cell carcinoma, esophageal adenocarcinoma, and cardia adenocarcinoma. We studied familial aggregation by the family history method (3) in a large, population-based case-control study in Sweden.

Materials and Methods

Design. A detailed description of the study has been published elsewhere (4). In brief, during 1995 through 1997, all patients with newly diagnosed adenocarcinoma of the esophagus or gastric cardia and half of the patients with esophageal squamous cell carcinoma (born on even dates) in the entire Swedish population <80 years of age were eligible as cases. A comprehensive organization with collaboration with all relevant hospital departments and all regional tumor registries in Sweden ensured that every case throughout the country was identified shortly after diagnosis. Cases were uniformly classified histologically and anatomically, and the histological slides were reviewed by the study pathologist. At endoscopy, serial biopsies were obtained to identify the tumor site and the occurrence of intestinal metaplasia of the stomach or the esophagus (Barrett's esophagus). Surgeons and pathologists gave standardized, detailed descriptions of the location of resected tumors. Adenocarcinomas were classified as cardia cancers if the tumor center was within 2 cm proximal or 3 cm distal to the gastroesophageal junction. Control subjects were randomly selected from the Swedish population register and frequency-matched to resemble the age and sex distribution among the cases.

Data Collection. All subjects underwent computer-aided face-to-face interviews by professional interviewers from Statistics Sweden. Questions were asked about the occurrence and type of cancer among biological parents, siblings, and children. We did not ask for the relatives National Registration Numbers, a 10-digit unique personal identifier assigned to all Swedish residents, because it was unlikely for subjects to recall this number. Information was collected about potential confounders. In multivariate analyses, we adjusted for age (in 5-year classes), sex, number of biological siblings (continuous), reflux symptoms (occurring at least once per week), body mass index (in quartiles), tobacco smoking (assessed 2 years before the interview and classified into never smoker, previous smoker, and current smoker of any tobacco), alcohol use (total amount of alcohol consumed categorized in four classes), socioeconomic status (years of formal education categorized in three classes), energy intake (categorized in three classes), intake of fruits and vegetables (categorized in three classes), and physical activity (categorized in four classes).

Statistical Analyses. Logistic regression was used in univariate and multivariate modeling. Model parameters were esti-

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Table 1 Selected cancers among first-degree relatives and the risk of adenocarcinoma of the esophagus, adenocarcinoma of the gastric cardia, and squamous cell carcinoma of the esophagus

Cancer site among first-degree relatives	Adenocarcinoma of the esophagus			Adenocarcinoma of the gastric cardia		Squamous cell carcinoma of the esophagus	
	Controls	Cases	OR ^a (95% CI)	Cases	OR ^a (95% CI)	Cases	OR ^a (95% CI)
Esophagus							
No	797	183	1.0 (reference)	256	1.0 (reference)	166	1.0 (reference)
Yes	19	6	1.4 (0.5–4.1)	6	0.9 (0.4–2.5)	1	0.2 (0.0–1.5)
Stomach (cardia cancer included)							
No	745	176	1.0 (reference)	227	1.0 (reference)	149	1.0 (reference)
Yes	71	13	0.8 (0.4–1.6)	35	1.6 (1.0–2.6)	18	1.2 (0.7–2.3)
Gastrointestinal tract ^b							
No	647	151	1.0 (reference)	199	1.0 (reference)	129	1.0 (reference)
Yes	169	38	1.0 (0.6–1.5)	63	1.3 (0.9–1.8)	38	1.0 (0.6–1.6)
Lung							
No	777	180	1.0 (reference)	252	1.0 (reference)	151	1.0 (reference)
Yes	39	9	1.5 (0.6–3.6)	10	0.8 (0.4–1.8)	16	2.3 (1.1–4.6)
Breast							
No	774	178	1.0 (reference)	239	1.0 (reference)	156	1.0 (reference)
Yes	42	11	0.8 (0.4–2.0)	23	2.0 (1.1–3.5)	11	1.1 (0.5–2.4)
Prostate							
No	781	182	1.0 (reference)	248	1.0 (reference)	160	1.0 (reference)
Yes	35	7	1.1 (0.4–2.9)	14	1.7 (0.8–3.3)	7	1.3 (0.5–3.4)
Gynecological							
No	776	178	1.0 (reference)	251	1.0 (reference)	163	1.0 (reference)
Yes	40	11	1.4 (0.6–3.3)	11	0.9 (0.4–1.9)	4	0.6 (0.2–1.9)
Any location							
No	461	98	1.0 (reference)	133	1.0 (reference)	81	1.0 (reference)
Yes	355	91	1.3 (0.9–1.9)	129	1.3 (1.0–1.8)	86	1.3 (0.9–1.9)

^a ORs were adjusted for: age, sex, reflux symptoms, body mass index, number of siblings, socioeconomic status, tobacco smoking, alcohol intake, consumption of fruits and vegetables, energy intake, and physical activity.

^b The tumors included in the gastrointestinal tract were located in the esophagus, cardia, stomach, small bowel, large bowel including the rectum, liver, gall bladder, and pancreas.

mated by the maximum likelihood method. From these estimates, ORs³ with 95% CIs were calculated. In multivariate modeling, adjustments were made for the 11 potential confounding variables mentioned above. The possibility of interaction between a family history of cancer and all of the variables listed above was tested in a multiplicative model with cross-product terms representing the interaction. Among 33 tests of interactions between heredity and the variables listed, the only significant effect was found between cancer heredity and reflux symptoms among esophageal squamous cell carcinoma cases. Because reflux symptoms are not associated with squamous cell carcinoma and our multiple testing increases the likelihood of chance findings, this effect was deemed to be an effect of chance. From here on in the text, we do not take interaction into further consideration.

Ethics. The study was approved by all regional ethics committees in Sweden. Individual informed consent to participate was obtained.

Results

Subjects. We interviewed 189 cases with esophageal adenocarcinoma, 262 with cardia adenocarcinoma, and 167 with esophageal squamous cell carcinoma. These constituted 87, 83, and 73%, respectively, of all eligible cases in the study base. Physical or mental disorders or early death prevented participation in 12–22% of the case groups and unwillingness in 1–5%. The 820 population-based control subjects constituted

73% of all who had been selected; 19% declined to participate, 6% had physical or mental disorders, and 2% could not be traced. The proportions of men among the cases of esophageal adenocarcinoma, cardia adenocarcinoma, and esophageal squamous cell carcinoma were 87, 85, and 72%, respectively, and among the control subjects, 83%. The median ages in these groups were 69, 66, 67, and 68 years, respectively.

Adenocarcinoma of the Esophagus. There was no statistically significant association between a positive history of esophageal cancer among first-degree relatives and the risk of esophageal adenocarcinoma among our study subjects. Neither did we identify any association between familial occurrence of cancer of the gastrointestinal tract at any site or at all sites combined (Table 1). No individual tumor site among relatives was significantly associated with the risk of esophageal adenocarcinoma. There was no association found among subjects who reported more than one first-degree relative with cancer (data not shown). No cases and only one control subject reported more than one first-degree with esophageal cancer. The age- and sex-adjusted estimates (data not shown) remained virtually unchanged after adjustment for all 11 covariates presented in “Materials and Methods,” indicating absence of substantial confounding by these factors.

Adenocarcinoma of the Gastric Cardia. Patients with cancer of the gastric cardia did not report familial occurrence of esophageal cancer more often than controls, but they indicated a moderate excess of gastric cancer (including cardia cancer) among their first-degree relatives (Table 1). The adjusted OR for cardia cancer among subjects with a positive gastric cancer family history, relative to those without, was 1.6 (95% CI,

³ The abbreviations used are: OR, odds ratio; CI, confidence interval.

1.0–2.6). One cardia cancer case and six control subjects had two or more first-degree relatives with stomach cancer. No case, but one control, reported multiple occurrences of esophageal cancer in the family. The risk of cardia cancer was increased among persons who reported having a first-degree relative with breast cancer (OR, 2.0; 95% CI, 1.1–3.6). No associations were found with cancer of other sites (Table 1). The age- and sex-adjusted and multivariately adjusted relative risk estimates were very similar (data not shown).

Squamous Cell Carcinoma of the Esophagus. There was no increased risk of esophageal squamous cell carcinoma among persons with relatives with esophageal cancer or other cancers of the gastrointestinal tract (Table 1). The only statistically significant association was found among persons who reported a first-degree relative with a history of lung cancer (OR, 2.3; 95% CI, 1.1–4.7). About 2% (4 of 167) of the cases with squamous cell carcinoma reported more than one first-degree relative with gastric cancer. None had multiple occurrences of esophageal cancer in their families. We did not identify any increased risk when all types of cancer among relatives were combined. Multivariate adjustment did not substantially change the age- and sex-adjusted risk estimates (data not shown).

Discussion

We found no important association between a family history of esophageal cancer and risk of this cancer, regardless of histological type. In contrast, patients with gastric cardia cancer reported a family history of gastric cancer more often than controls.

In contrast to our findings, several epidemiological studies in endemic areas in China have demonstrated excess risk of esophageal cancer (mainly squamous cell carcinoma) among members of families with a history of such cancers (5–9). Case-control studies have yielded ORs of 1.6–6.0 among persons with esophageal cancer in the family (5, 6, 8). Confounding by family-specific environmental or lifestyle factors may, however, explain these associations. A case-control study of unspecified esophageal cancer from a Western high-incidence population (North Carolina) did not identify any familial link (10), and in a study conducted in a low-incidence population (New York; Ref. 11), none of 139 male patients with esophageal squamous cell carcinoma had a family history. It is possible that many esophageal cancers in Asian high-risk populations represent an etiologically distinct disease entity, an assumption supported by the absence of associations with Western risk factors such as male sex, smoking, and alcohol use (2). At least for the “Western type” of esophageal squamous cell carcinoma, it appears that genetic factors play a minor role.

A small American case-control study found no association between a history of any cancer in first-degree relatives and risk of esophageal and gastric cardia adenocarcinoma combined (12), which is in agreement with our results. An Italian case-control study with 68 cases of cardia cancer found essentially no increase in risk among cases with one first-degree relative with gastric cancer (OR, 1.2), but two or more such relatives introduced an 8-fold increased risk (13). This observation, like our findings, indicate that a genetic link with gastric cancer may exist.

Strengths of our study include the almost complete, nationwide inclusion of patients during a 3-year period and strict random sampling of control subjects from our well-defined study base, making this a truly population-based investigation. The thorough tumor classification allowed us to isolate histological type-specific associations. All subjects were inter-

viewed personally, and the interviews provided information of potential confounding.

Weaknesses include possible misclassification of cancers in relatives and a limited statistical precision because of the rarity of the studied cancers, weaknesses that our study shares with all previous studies. We could not objectively confirm the reported cancer among relatives because the National Registration Numbers were not available for matching with the Swedish Cancer Register. The accuracy of laymen’s reports of cancer occurrence in first-degree relatives has been shown to be acceptable for some cancers (14–16) but more questionable for others, including abdominal cancers (15, 17, 18). Because the Swedish word “mage” means both stomach and abdomen, gastric cancer may be confused with other intra-abdominal malignancies. Esophageal cancers are probably less likely to be confused with other cancers, but there are no data to substantiate this assumption. Nondifferential misclassification, *i.e.*, errors that occur independently of case/control status, generally biases the ORs toward the null (19). Because the error rate varies by the closeness of the relationship (14, 17, 18), we restricted our inquiries to first-degree relatives, and it is unlikely that strong associations were canceled by nondifferential misclassification.

Data about cardia cancer, an entity that is unknown to most people, must be interpreted with skepticism. Among our subjects, the only ones aware of the existence of the specific cardia cancer disease were case patients with a cardia cancer diagnosis, thus producing a possibly spurious association. In the analysis of cardia cancer patients, we therefore combined cardia cancer with all gastric cancer among relatives.

Different recollections among cases and controls would probably inflate the estimates, because patients with cancer are likely to tax their memories for previous occurrences of cancers in the family more than healthy control subjects. Although such recall bias is generally of minor importance in first-degree relatives (15, 17), the excess risk of cardia cancer among subjects with a family history of gastric cancer may partly be explained by such bias.

Because the subjects were generally unaware of the distinction between adenocarcinomas and squamous cell carcinomas, it was impossible for us to evaluate histological type-specific heredity for these tumors. If such heredity would exist, for instance if patients with esophageal adenocarcinoma would have an excess of family histories of adenocarcinomas, these patients would also have some excess of family histories of all esophageal cancer, however.

We found no substantial confounding by any of the studied covariates. Residual confounding by smoking could, however, explain the association found between familial lung cancer and esophageal squamous cell carcinoma. Tobacco smoking is strongly associated with both these tumors, and smoking is more common among persons with first-degree relatives who smoke (20).

There is no obvious biological mechanism that could explain the unexpected finding of an association between familial breast cancer and the risk of cardia cancer. Chance may explain this finding. A similar tendency toward association was, however, observed by Zhang *et al.* (12).

Familial clustering of Barrett’s esophagus and gastroesophageal reflux disease, with or without esophageal adenocarcinoma, has been described (21–23), and there are indications of a genetic predisposition as a component in the etiology of reflux disease and its complications (21, 24). Because reflux and Barrett’s esophagus are strongly linked with esophageal adenocarcinoma (4), any hereditary components in reflux dis-

ease and Barrett's esophagus would probably shine through in the pattern of occurrence of esophageal adenocarcinoma. Our null findings with regard to heredity in this cancer type provides indirect evidence that putative hereditary forms of reflux and Barrett's esophagus do not have substantial impact on the occurrence of esophageal adenocarcinoma in Sweden.

In conclusion, important genetic components are unlikely in the etiologies of esophageal adenocarcinoma or squamous cell carcinoma in Sweden. Nondifferential misclassification may, however, have canceled weak associations between a positive family history and risk in our study. Although recall bias cannot be ruled out as the explanation for the association between a family history of gastric cancer and risk of cardia cancer, this association also has been reported previously and may therefore be real.

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