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Family History of Cancer, Its Combination with Smoking and Drinking, and Risk of Squamous Cell Carcinoma of the Esophagus

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Abstract

We analyzed the association between history of cancer in first-degree relatives and the risk of squamous cell carcinoma of the esophagus (SCCE) using data from three case-control studies conducted in Italy and Switzerland on 805 incident, histologically confirmed SCCE, and 3,461 hospital controls. The alcohol- and tobacco-adjusted odds ratio (OR) for a family history of esophageal cancer was 3.2 [95% confidence interval (CI), 1.7-6.2], and the OR was higher when the affected relative was a brother or was diagnosed at age <55 years. Compared to subjects without family history of esophageal cancer, noncurrent smokers, drinking <49 drinks per week, the OR was 2.9 (95% CI, 1.1-7.5) for family history alone, 15.5 (95% CI, 11.7-20.5) for current smokers drinking ≥49 drinks per week without family history of esophageal cancer, and 107.0 (95% CI, 13.0-880.2) for current smokers drinking ≥49 drinks per week who also had a family history of esophageal cancer. The risk of SCCE was also increased in subjects with a family history of cancer of the oral cavity/pharynx (OR, 3.7; 95% CI, 1.5-9.0) and stomach (OR, 2.0; 95% CI, 1.1-3.6), but not of other cancers, nor for a family history of any cancer (OR, 1.0; 95% CI, 0.8-1.4). These data show that, as for many other epithelial cancers, the risk of SCCE is increased in subjects with a family history of the disease, and that—in Western countries—avoidance of alcohol and tobacco is also the best way to prevent SCCE in subjects with a family history of the disease. (Cancer Epidemiol Biomarkers Prev 2005;14(6):1390–3)

Introduction

Esophageal cancer rates show a >300-fold geographical variation worldwide, with the highest rates recorded in some areas of China and central Asia, and in most populations, the vast majority of esophageal cancers are squamous cell carcinomas of the esophagus (SCCE; ref. 1). In Europe and North and South America, tobacco and alcohol—and possibly a diet poor in fruit and vegetables—explain the vast majority of SCCE (1, 2). In the high-risk areas of China and central Asia (as well as some areas of South America), nutritional deficiencies, and hot food and drinks are the major determinants (1). Although important environmental causes of SCCE in Western countries are well identified, it is still possible that genetic or other endogenous factors may also influence susceptibility to this cancer (3).

Several epidemiological studies from high-risk areas in China and the Caspian Littoral of Iran found that esophageal/gastric cancer aggregates in families, and that a family history of esophageal/gastric cancer is a risk factor for the disease (4-11). Results have been less consistent in studies from other areas of the world. No association between family history of esophageal cancer and risk of SCCE was found in three case-control studies from the U.S. (12, 13) and Sweden (14), including about 200 cases each. Conversely, a case-control study from Japan on 167 cases with squamous cell carcinoma of the hypopharynx or cervical esophagus found an odds ratio (OR) of 5.1 [95% confidence interval (CI), 0.7-36.1] in subjects with a family history of esophageal cancer, and an OR of 2.6 (95% CI, 1.1-6.3) for a family history of cancers of the esophagus, head and neck or lung (15). The Swedish Family-Cancer Database, which includes 10.1 million individuals and about 6,000 cases with esophageal cancers, found a standardized incidence ratio of 4.9 (95% CI, 1.8-9.6) for having a parent with SCCE, and of 12.6 (95% CI, 1.2-36.2) for having a SCCE in a sibling (16).

To provide further data on the issue, we analyzed the association between family history of cancer in first-degree relatives, its relation with alcohol and tobacco, and the risk of SCCE using data from three case-control studies conducted in Italy and Switzerland in the 1980s and 1990s.

Materials and Methods

The current analysis is based on data from three case-control studies of SCCE (17-20). The first study (study I) was conducted between 1984 and 1992 on 316 cases and 1,544 controls, in the greater Milan area (17); the second (study II) between 1985 and 1992 on 94 cases and 851 controls, in the Province of Pordenone (18), and the third (study III) between 1992 and 1997 on 395 cases and 1,066 controls, in the provinces of Pordenone, Milan and Padua, and in the Swiss canton of Vaud (19, 20).

Details on the individual studies have been published elsewhere (17-20). In all studies, cases were subjects admitted to the major teaching and general hospitals in the areas under study with incident, histologically confirmed SCCE, diagnosed no longer than 1 year before the interview, and with no history of cancer. A total of 805 subjects were included in this analysis (694 men and 111 women), whose median age was

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60 years (range 26-83 years). Controls were subjects admitted to the same hospitals as the cases for a wide spectrum of acute, nonneoplastic conditions, not related to smoking or alcohol consumption or long-term modifications of diet. In study III, cases and controls were frequency-matched on age (5-year groups), sex and area of residence. In all three studies, <5% of the identified controls refused or were unable to participate. The control group comprised a total of 3,461 subjects (2,682 men and 779 women), whose median age was 58 years, ranging between 25 and 84 years. Twenty-six percent of the controls were admitted for traumas, 23% for other nontraumatic orthopedic conditions, 33% for acute surgical conditions, and 18% for miscellaneous other illnesses, including eye, nose, ear, skin, or dental disorders.

Although the questionnaires of the three studies differed, cases and controls were always interviewed during their hospital stay by trained interviewers, using a structured questionnaire that included information on sociodemographic characteristics, anthropometric measures, lifestyle habits (including tobacco smoking and alcohol drinking), and a dietary section of varying length. The section on family history differed in detail in the three studies. In study I, only one question investigated whether a first-degree relative had ever been diagnosed with esophageal cancer, with no indication of the relative affected. In study II, the total number of brothers and sisters, and whether a parent or one or more siblings had ever had a cancer of the esophagus or of other organs of the digestive and respiratory tract was recorded. In study III, the subjects were specifically asked how many sisters and brothers they had, and whether their parents, siblings, children, grandparents or spouse had ever had any cancer (excluding nonmelanoma skin cancer). For each relative with a history of cancer, the subject was asked to report the vital status of the relative at the time of interview, his/her current age or the age at death, the site of the tumor and the age at cancer diagnosis. In the present analysis, we considered the history of cancer in first-degree relatives only, i.e., parents, siblings, and children. No verification of the self-reported cancer diagnoses in the relatives was done. In all three studies, ever smokers were individuals who had smoked at least one cigarette, cigar, or pipe per day for at least 1 year, and alcohol drinkers were individuals who drank at least one alcoholic drink per week.

We estimated the OR of SCCE and the corresponding 95% CI according to family history of esophageal and other cancers in first-degree relatives using conditional multiple logistic regression models (21). The models were conditioned on study, sex, age (5-year groups), and study center (for study III, four centers), and further adjusted for years of education, tobacco smoking, alcohol drinking, and number of brothers and/or sisters. For study I, where the information on number of siblings was not available, the mean value was used. Additional adjustments for fruit and vegetable intake did not materially modify the estimates.

Results

Table 1 shows the risk of SCCE according to family history of esophageal cancers in first-degree relatives, separately for the three studies, and combined. A total of 25 cases (3.1%) and 28 controls (0.8%) reported a family history of esophageal cancer. None of the study subjects reported more than one esophageal cancer in first-degree relatives. The OR was 7.5 in study I, 2.6 in study II, and 2.3 in study III. The combined estimate was 3.6 (95% CI, 2.0-6.4), and became 3.2 (95% CI, 1.7-6.2) after further adjustment for education, smoking, alcohol, and number of brothers and sisters. When the affected relative was a parent of the proband, the pooled OR was 1.3 (95% CI, 0.4-4.3), whereas the corresponding OR for an affected sibling was 4.6 (95% CI, 1.2-17.4). In study III, the association was stronger when the relative was diagnosed before age 55 years (OR, 4.7) than above age 55 (OR, 1.6).

Table 2 gives the distribution of cases and controls according to family history of esophageal cancer in separate strata of sex, age, education, tobacco, and alcohol consumption, intake of fruit and vegetable, and the corresponding ORs. Although the association was apparently stronger in males (OR, 3.5), in subjects aged 60 or more years (OR, 5.1), in those with a higher education (OR, 6.6), in current smokers (OR, 5.6), and in those with a higher fruit intake, the OR was above unity in all strata and tests for interaction were not statistically significant for any of the strata considered.

The joint effect of smoking, drinking, and family history of esophageal cancer is shown in Fig. 1. Compared with the lowest risk category, i.e., never/ex-smokers, drinkers of <49 drinks per week without family history of esophageal cancer, the risk was significantly increased in those with one or more factors in the highest risk category. In particular, the OR was 2.9 (95% CI, 1.1-7.5) for family history alone, 15.5 (95% CI, 11.7-20.5) for current smokers drinking ≥49 drinks per week without family history of esophageal cancer, and 107.0 (95% CI, 13.0-880.2) for those who were smokers and heavy drinkers and also reported a first-degree relative with esophageal cancer (four cases and two controls). The three-way χ^2 for interaction was 6.40, with 4 *df* ($P = 0.17$).

Table 3 shows the distribution of cases and controls from study III according to history of other selected cancers in first-degree relatives, and the corresponding ORs. The risk of SCCE was significantly increased in subjects with a family history of

Table 1. OR of esophageal cancer according to family history of esophageal cancers in first-degree relatives in three studies from Northern Italy and Switzerland (1984-1997)

Family history of esophageal cancer	Study I		Study II		Study III		Pooled	
	Cases/ controls	OR* (95% CI)	Cases/ controls	OR* (95% CI)	Cases/ controls	OR* (95% CI)	OR* (95% CI)	OR† (95% CI)
No	304:1,537	1	92:844	1	384:1,052	1	1	1
Yes	12:7	7.5 (2.9-19.5)	2:7	2.6 (0.5-13.5)	11:14	2.3 (1.0-5.2)	3.6 (2.0-6.4)	3.2 (1.7-6.2)
Type of relative								
Parent	—	—	0:3	0	6:10	2.0 (0.7-5.2)	1.8 (0.7-4.8)	1.3 (0.4-4.3)
Sibling	—	—	2:4	3.6 (0.6-21.6)	4:4	3.2 (0.8-13.0)	3.3 (1.1-10.2)	4.6 (1.2-17.4)
Child	—	—	—	—	1:0	—	—	—
Age of affected relative (years)								
<55	—	—	—	—	5:3	4.7 (1.1-20.6)	—	—
≥55	—	—	—	—	6:11	1.6 (0.6-4.5)	—	—

*ORs conditioned on study, sex, age, and study center (when appropriate). Reference category: no family history of esophageal cancer.
†Further adjusted for education, smoking, alcohol, and number of brothers and sisters.

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Table 2. OR of esophageal cancer according to family history of esophageal cancers in strata of selected covariates (Italy and Switzerland, 1984-1997)

Stratum	Family history		OR* (95% CI)	OR† (95% CI)
	Cases/controls (No)	Cases/controls (Yes)		
Sex				
Males	672:2,663	22:19	4.1 (2.2-7.8)	3.5 (1.7-7.4)
Females	108:770	3:9	2.1 (0.5-8.4)	1.9 (0.4-9.9)
Age (years)				
<60	367:1,957	8:14	2.7 (1.1-6.7)	1.5 (0.5-4.4)
≥60	413:1,476	17:14	4.4 (2.1-9.2)	5.1 (2.2-11.7)
Education (years)				
<7	500:1,786	16:20	2.7 (1.3-5.5)	2.4 (1.1-5.3)
≥7	280:1,647	9:8	6.1 (2.1-17.9)	6.6 (1.9-23.4)
Smoking				
Never/former	301:2,191	10:23	2.8 (1.3-6.1)	2.5 (1.1-6.1)
Current	479:1,242	15:5	8.8 (2.8-28.0)	5.6 (1.6-19.5)
Alcohol (drinks/wk)				
<21	145:1,655	3:12	2.5 (0.7-9.3)	3.2 (0.8-12.2)
21 to <49	262:1,155	10:10	3.1 (1.2-8.0)	2.9 (1.1-7.9)
≥49	372:629	12:6	3.5 (1.1-10.8)	3.2 (1.0-10.5)
Fruit intake (portions/wk)				
≤7	506:1,600	11:10	3.7 (1.4-9.6)	2.0 (0.5-7.9)
>7	271:1,846	14:18	5.8 (2.7-12.4)	3.9 (1.2-13.0)
Vegetable intake (portions/wk)				
≤7	501:1,720	11:6	5.7 (2.0-16.0)	3.6 (1.0-13.3)
>7	267:1,656	14:21	4.0 (2.0-8.3)	3.9 (1.4-10.6)

*ORs conditioned on study, sex, age and study center (when appropriate). Reference category: no family history of esophageal cancer.
†Further adjusted for education, smoking, alcohol, and number of brothers and sisters.
‡The data do not sum up to the total because of some missing values.

Table 3. OR of esophageal cancer according to family history of selected cancers in first-degree relatives in study III (Italy and Switzerland, 1992-1997)

Cancer site	Subjects with family history (%)		OR* (95% CI)	OR† (95% CI)
	Cases	Controls		
Oral cavity/pharynx	19 (5.8)	13 (1.2)	4.6 (2.2-9.5)	3.7 (1.5-9.0)
Stomach	30 (7.6)	38 (3.6)	2.3 (1.4-3.8)	2.0 (1.1-3.6)
Intestines	18 (4.6)	49 (4.6)	1.0 (0.6-1.7)	1.1 (0.5-2.0)
Liver	14 (3.5)	30 (2.8)	1.2 (0.6-2.4)	0.7 (0.3-1.5)
Larynx	3 (0.8)	15 (1.4)	0.7 (0.2-2.4)	0.7 (0.2-2.8)
Lung	30 (7.6)	63 (5.9)	1.4 (0.9-2.2)	0.9 (0.5-1.6)
Breast	12 (3.0)	42 (3.9)	0.8 (0.4-1.6)	0.9 (0.4-1.9)
Uterus	9 (2.3)	21 (2.0)	1.1 (0.5-2.5)	1.3 (0.5-3.2)
Pancreas	5 (1.3)	17 (1.6)	0.9 (0.3-2.5)	0.7 (0.2-2.0)
Prostate	4 (1.0)	18 (1.7)	0.7 (0.2-2.0)	0.8 (0.2-2.7)
Leukemias	4 (1.0)	16 (1.5)	0.7 (0.2-2.2)	1.0 (0.2-3.9)
All sites	145 (36.7)	349 (32.7)	1.3 (1.0-1.6)	1.0 (0.8-1.4)

*ORs conditioned on study, sex, age and study center (when appropriate). Reference category: no family history of esophageal cancer.
†Further adjusted for education, smoking, alcohol, and number of brothers and sisters.

oral/pharyngeal cancer (OR, 3.7; 95% CI, 1.5-9.0), and stomach cancer (OR, 2.0; 95% CI, 1.1-3.6), but not for a family history of any other cancer. The OR for all sites combined was 1.0 (95% CI, 0.8-1.4).

Discussion

In this uniquely large data set of three case-control studies from Italy and Switzerland, the risk of SCCE was increased 3-fold in individuals with a first-degree relative diagnosed with esophageal cancer, and the risk was further enhanced by exposure to alcohol and tobacco. Also, a family history of oral/pharyngeal and stomach cancer seemed to increase the risk of SCCE.

To limit potential sources of bias (21), we carefully selected controls admitted for diseases unrelated to tobacco smoking and alcohol drinking, the catchment area of cases and controls was comparable, participation rates of both cases and controls were high, and strict control of confounding for tobacco and alcohol, as well as family size (for studies II and III), was done. Although studies I and II were not matched on sex, and there was some imbalance between cases and controls, the use of conditional logistic regression has implied stratification by sex in the estimation of the ORs, thus avoiding confounding by sex.

Information on family history was self-reported, and it is possible that cases were more aware than controls of a history

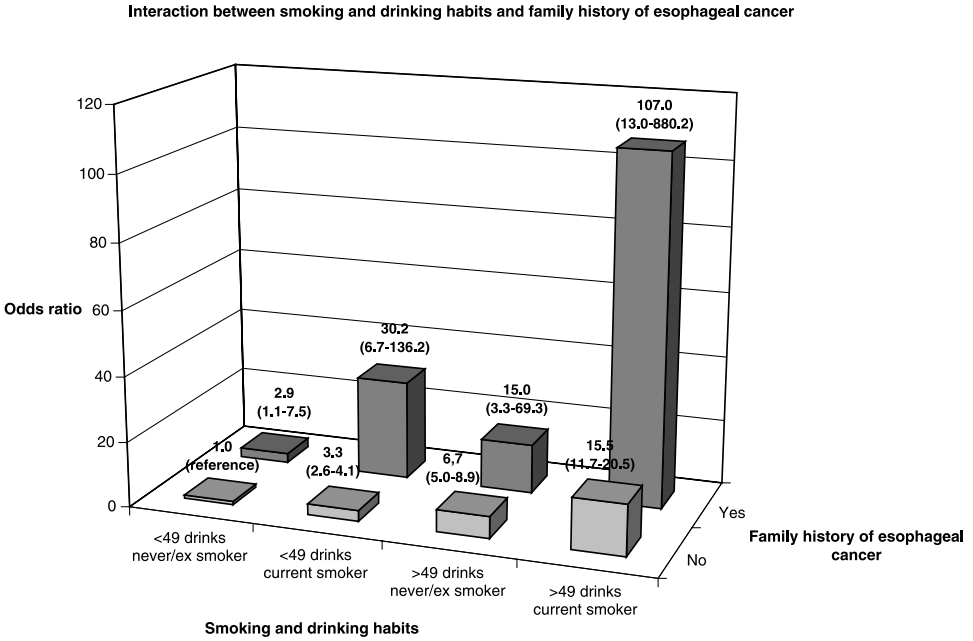

Figure 1. OR of SCCE according to smoking, drinking, and family history of esophageal cancer. Estimates from conditional logistic regression models conditioned on study, sex, age, and study center and adjusted for education and number of brothers and sisters. The number of cases/controls in the four categories from left to right were: for no family history of esophageal cancer 246:957, 246:957, 139:342, and 233:290; and for positive family history of esophageal cancer 6:19, 7:3, 4:4, and 8:2.

of cancer in the family. The similar hospital setting of the interview should, however, have improved comparability of the information collected (22). Moreover, in study III, the OR for a family history of any cancer was 1.0, suggesting that differential reporting of familial cancer in general did not occur. Finally, a similar—or even stronger—association was found in the Swedish Family-Cancer Database (16), a linkage study not affected by the above mentioned biases.

For many common cancers, including cancers of the digestive tract, and smoking- and alcohol-related cancers, first-degree relatives of affected individuals have a 2- to 5-fold increased risk of developing a cancer at the same site (23, 24). This study provides quantitative evidence that such an association is of similar magnitude for cancer of the esophagus.

Also in agreement with the Swedish Family-Cancer Database results, in our study, the risk was higher when the affected relative was a sibling, rather than a parent. This suggests that recessive or X-linked susceptibility genes may be involved (25).

The subjects in our study reported at most one first-degree relative with esophageal cancer, suggesting that highly penetrant esophageal cancer susceptibility genes are extremely rare in this population, if existent at all (23). However, we have investigated family history only in first-degree relatives, and thus there was only a small number of subjects at risk in each family. The mean number of siblings in studies II and III was 3.8, similar for cases and controls.

The risk of SCCE was increased for a family history of oral/pharyngeal and stomach cancer. It is possible that some misclassification between contiguous parts of the digestive tract has occurred in reporting cancer in the relatives. In Western countries, however, cancers of the oral cavity/pharynx and SCCE show remarkable similarities in etiology and geographic distribution (26). Moreover, synchronous and metachronous cancers in both the esophagus and the oral cavity and pharynx have been observed (16, 27-29). Familial aggregation of SCCE and oral/pharyngeal cancers may be due to shared environmental exposure to the main risk factors, i.e., alcohol and tobacco. However, the risk of SCCE was not increased in individuals with a family history of cancer at other sites related to smoking (lung), alcohol (liver) or both factors (larynx). A joint inherited susceptibility to both cancers, thus, cannot be ruled out. Similarly, in high-risk areas of China, cancers of the esophagus and the gastric cardia are both very frequent, and a link between the two is conceivable (11).

The analysis of the joint effect with alcohol and tobacco found that (*a*) family history was also a risk factor in subjects with relatively low exposure to tobacco (never or ex-smokers) and alcohol (≤21 drinks per week), and (*b*) it seemed to act in a multiplicative way with alcohol and tobacco. Given the small number of cases of SCCE in these categories, we could not investigate the role of family history in subjects not exposed to either tobacco or alcohol. The ORs of family history, however, were virtually identical in all strata of alcohol consumption. Conversely, they were higher in current smokers, although the test for interaction was not statistically significant. If anything, the relation with smoking seemed even supra-multiplicative. Given the small numbers, these results must be interpreted with due caution. It is possible, however, that—at least in some families—what is inherited is a higher susceptibility of the esophageal epithelium to the damages of smoking. In any case, this study clearly indicates that, for individuals with a family history of esophageal cancer, the most effective way to prevent SCCE is to avoid alcohol and tobacco.

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