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ORIGINAL CONTRIBUTION

Diet-related inflammation and oesophageal cancer by histological type: a nationwide case–control study in Sweden

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Abstract

Purpose This project sought to test the role of diet-related inflammation in modulating the risk of oesophageal cancer.
Methods A nationwide population-based case–control study was conducted from 1 December 1994 through 31 December 1997 in Sweden. All newly diagnosed patients with adenocarcinoma of the oesophagus or gastroesophageal junction and a randomly selected half of patients with oesophageal squamous cell carcinoma were eligible as cases. Using the Swedish Registry of the Total Population, the control group was randomly selected from the entire Swedish population and frequency-matched on age (within 10 years) and sex. The literature-derived dietary inflammatory index (DII) was developed to describe the inflammatory potential of diet. DII scores were computed based on a food frequency questionnaire. Higher DII scores indicate more pro-inflammatory diets. Odds ratios and 95 % confidence intervals (CI) were computed to assess risk associated between DII scores and oesophageal cancer using logistic regression adjusted by potential confounders.
Results In total, 189 oesophageal adenocarcinomas, 262 gastroesophageal junctional adenocarcinomas, 167 oesophageal squamous cell carcinomas, and 820 control subjects were recruited into the study. Significant associations with DII were observed for oesophageal squamous cell carcinoma ($OR_{Quartile4vs1}$ 4.35, 95 % CI 2.24, 8.43), oesophageal adenocarcinoma ($OR_{Quartile4vs1}$ 3.59, 95 % CI 1.87, 6.89), and gastroesophageal junctional adenocarcinoma ($OR_{Quartile4vs1}$ 2.04, 95 % CI 1.24, 3.36). Significant trends across quartiles of DII were observed for all subtypes of oesophageal cancer.
Conclusions Diet-related inflammation appears to be associated with an increased risk of oesophageal cancer, regardless of histological type.

Keywords Diet · Inflammation · Neoplasm · Oesophagus

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Introduction

The incidence of adenocarcinoma of the oesophagus or gastroesophageal junction has risen at an alarming rate in Western populations over the past four decades, while rates of oesophageal squamous cell carcinoma, which were much higher relative to adenocarcinomas decades ago, have remained steady for many decades [1, 2]. Oesophageal adenocarcinoma arises from glandular cells of the lower third of the oesophagus, while squamous cell carcinoma of the oesophagus originates from the epithelial cells.

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They are therefore characterised by distinct risk factor profiles and occur with varying epidemiologic patterns in different regions of the world.

Epidemiologic evidence has shown that chronic inflammation is important in triggering the development of oesophageal cancer. This is especially evident in the obesity-driven, low-grade inflammation seen most strongly in oesophageal adenocarcinoma. However, inflammation also is associated with the epithelial damage observed in both oesophageal cancer subtypes [3]. Inflammation has been implicated in oesophageal carcinogenesis through processes known to be associated with a variety of risk factors, including obesity [4], gastroesophageal reflux [5], smoking [6], the microbiome (*e.g. human papillomavirus*) [7], and diet [8]. Consistently, diet has been shown to modulate inflammation [9]. Nutrients such as phytoestrogens, fibre, and folate possess anti-inflammatory properties that may offer protection against oesophageal cancer; while food/nutrients such as processed meat, saturated fat, and compounds that can be metabolised from foods, such as dietary *N*-nitrosomethylbenzylamine, which are known to increase inflammation, may increase the risk [10–12]. Although the anti- or pro-inflammatory properties of food or nutrients are established, it is unclear how they function in the development of oesophageal cancer. Until now, due to the difficulty in measuring the inflammatory effects of food or nutrients, few studies have examined single food or nutrient-related inflammation and oesophageal cancer risk [8, 13]. More importantly, no study has employed a measure of diet-related inflammation based on the whole diet.

The dietary inflammation index (DII), a literature review-based composite scoring system, was developed to reflect the potential inflammatory effects of diet (including whole foods, nutrients, and bioactive compounds). The DII scoring system was originally developed in 2009 [14] and updated by members of our group in 2013 [15]. In the updated version, nearly 2000 papers were reviewed and scored, and 45 food parameters, including foods, nutrients, and other bioactive compounds, were evaluated based on their inflammatory effects associated with these specific inflammatory markers: interleukin (IL)-1, IL-4, IL-6, IL-10, tumour necrosis factor (TNF)-α, and C-reactive protein (CRP) [15]. Higher DII scores indicate more pro-inflammatory diets. The DII scoring system has been validated with various inflammatory markers, including CRP [16] and interleukin-6 [17].

In this study, we examined the association between DII scores, used as a composite index for diet-associated inflammation, and the risk of oesophageal cancers in a nationwide case–control study in Sweden.

Methods

Study design

This was a nationwide, population-based case–control study that has been described in detail previously [5]. In brief, oesophageal cancer cases and controls were recruited and data collected from 1 December 1994 through 31 December 1997 based on the entire Swedish-born population (between 19 and 80 years of age). Eligible for inclusion in the study were all patients with newly diagnosed adenocarcinoma of the oesophagus or gastroesophageal junction, and a random selection (from individuals born on even-numbered days) of patients with oesophageal squamous cell carcinoma. The reason for such a sampling strategy was due to the following: (1) the main objective of the designed case–control study at that time was to investigate risk factors for adenocarcinoma of the oesophageal and gastroesophageal junction; (2) the incidence of squamous cell carcinoma was higher than that of adenocarcinoma during the inclusion period; and (3) there was limited funding to support the recruitment and data collection efforts in the light of cost-effective considerations [5]. Approximately, 87 % of cases of oesophageal adenocarcinoma, 65 % of adenocarcinoma of gastroesophageal junction, and 76 % of squamous cell carcinoma (when considering the specific sampling for squamous cell carcinoma) were recruited into this nationwide case–control study. The total participation rate exceeded 80 %. All cases were thoroughly and uniformly classified regarding histology and anatomic location of the cancer. The control group was randomly selected from the entire Swedish population and frequency-matched on age (within 10 years) and sex, using the Swedish Registry of the Total Population. All participants provided both written and verbal informed consent to participate in the study, which was approved by all six regional ethical review boards in Sweden including Umeå, Uppsala, Stockholm, Linköping, Göteborg, and Lund (registration numbers: 42/93 and 34-2819/2003).

Identification of cancer cases

A rapid ascertainment system to identify cases was used to ensure coverage of every potential case throughout the country. All 195 Swedish hospital departments involved in the diagnosis or treatment of oesophageal cancer collaborated in the recruitment of cases. The six Swedish Regional Tumor Registries enabled us to identify missing cases. There was a protocol for uniform documentation and classification of the tumours [5].

Data collection

Professional interviewers from Statistics Sweden (a governmental agency) personally interviewed all cases and controls to collect data on background variables and various exposures. Patient interviews mostly occurred shortly (within a few weeks; 90 % of the interviews were completed within 8 weeks after the first diagnosis) after diagnosis in order to minimise memory bias or the possibility of changes to lifestyle and dietary behaviours as a result of the diagnosis. Dietary data were collected using a food frequency questionnaire (adopted from a validated standard questionnaire) to assess habitual intake of 63 foods and beverages [18]. The questions were directed at dietary habits 20 years before the interview, with the purpose of obtaining a plausible induction time between the exposure and the diagnosis of invasive cancer. Missing answers or other uncertainties were clarified and, to the fullest extent possible, reconciled during these interviews. The intake frequency of each food item was assessed based on open answers, i.e. frequency of consumption (per day, week, month, or year). Dietary intake of each food item was calculated by multiplying the frequency of consumption by its sex-specific portion size, using data from the National Diet Survey [19]. Nutrients were calculated based on the food content tables provided by the Swedish Food Agency [20]. These included total, monounsaturated, saturated, trans-, omega-3, and omega-6 polyunsaturated fats; protein; carbohydrates; cholesterol; vitamins A, B6, B12, C, D, and E; beta carotene, thiamine, niacin, folate, riboflavin, fibre, caffeine, flavonoids, anthocyanidins, isoflavones; iron, magnesium, selenium, and zinc.

The dietary inflammatory index (DII)

A detailed description of how DII scores are calculated has been published elsewhere [15]. To briefly summarise, the dietary data were first linked to a regionally representative global database that we developed, which provided an estimate of a mean and standard deviation for each of the food parameters (i.e. foods, nutrients, and other food components such as flavonoids). A z score was then derived by subtracting the "standard global mean" from the amount reported and dividing this value by the standard deviation [15]. To minimise the effect of "right skewing" (a common occurrence with dietary data), this value was then converted to a centred percentile score, which was multiplied by the respective food parameter effect score (derived from a literature review and scoring of 1943 articles) to obtain each subject's food parameter-specific DII score. All of the food parameter-specific DII scores were summed to create the overall DII score for every subject in the study. $DII = b1 \times n1 + b2 \times n2 \cdots b36 \times n36$, where b refers to the literature-derived inflammatory effects score for each of the evaluable food parameters and n refers to the food parameter-specific centred percentiles, which were derived from the dietary data. A higher DII score indicates a more pro-inflammatory diet, which included all possible food/nutrients listed on the food frequency questionnaire. A validation of the DII score, based on both dietary recalls and a structured questionnaire (the seven-day dietary recall), similar to a food frequency questionnaire, has been published elsewhere [16]. A flow chart of the DII methodology is depicted in Fig. 1.

Statistical analysis

DII scores were analysed by quartiles in a manner consistent with our previous publications and other epidemiologic studies. Analyses based on tertiles and quintiles also were conducted, and results are provided as online supplemental materials (Supplemental Table 1-Supplemental Table 6). All categorisations (tertiles, quartiles, or quintiles) were based on the data distribution of the controls. Unconditional logistic regression was used to estimate odds ratios (ORs), with 95 % confidence intervals (95 % CIs). Age (<55, 55–64, 65–74, or ≥75 years) and sex (male or female) were adjusted in the basic models. In the full multivariable model, adjustments also were made for other potential risk factors for oesophageal squamous cell carcinoma and adenocarcinoma of the oesophagus and gastroesophageal junction. All of the covariates included in the full models were based on hypothetical aetiology of specific subtypes of oesophageal cancers. For oesophageal squamous cell carcinoma, the logistic model was further adjusted for tobacco smoking (never, always, or current smoker), alcohol use (gram equivalence of pure alcohol per week categorised in quartiles based on the consumption of the control participants), years of formal education (≤9 years, 10–12 years, or ≥13 years), and total energy intake. For adenocarcinoma of the oesophagus or gastroesophageal junction, two more potential confounders, gastroesophageal reflux (heartburn or regurgitation at least once a week occurring at least 5 years before the interview) and infection with *Helicobacter pylori* (*HP*) (HP+ and CagA+, HP+ or CagA+, or HP−) were added in the full model. In addition, interactions between body mass index [BMI = weight(kg)/height(m)^2] and the DII scores were examined. Because the results obtained were statistically significant, additional analyses, stratified on BMI, were performed and the results were displayed separately. p values for trend were computed using continuous value of the DII scores.

We excluded participants with >10 % missing values of dietary data from the final analysis. The distributions of sex and age did not differ between the excluded and
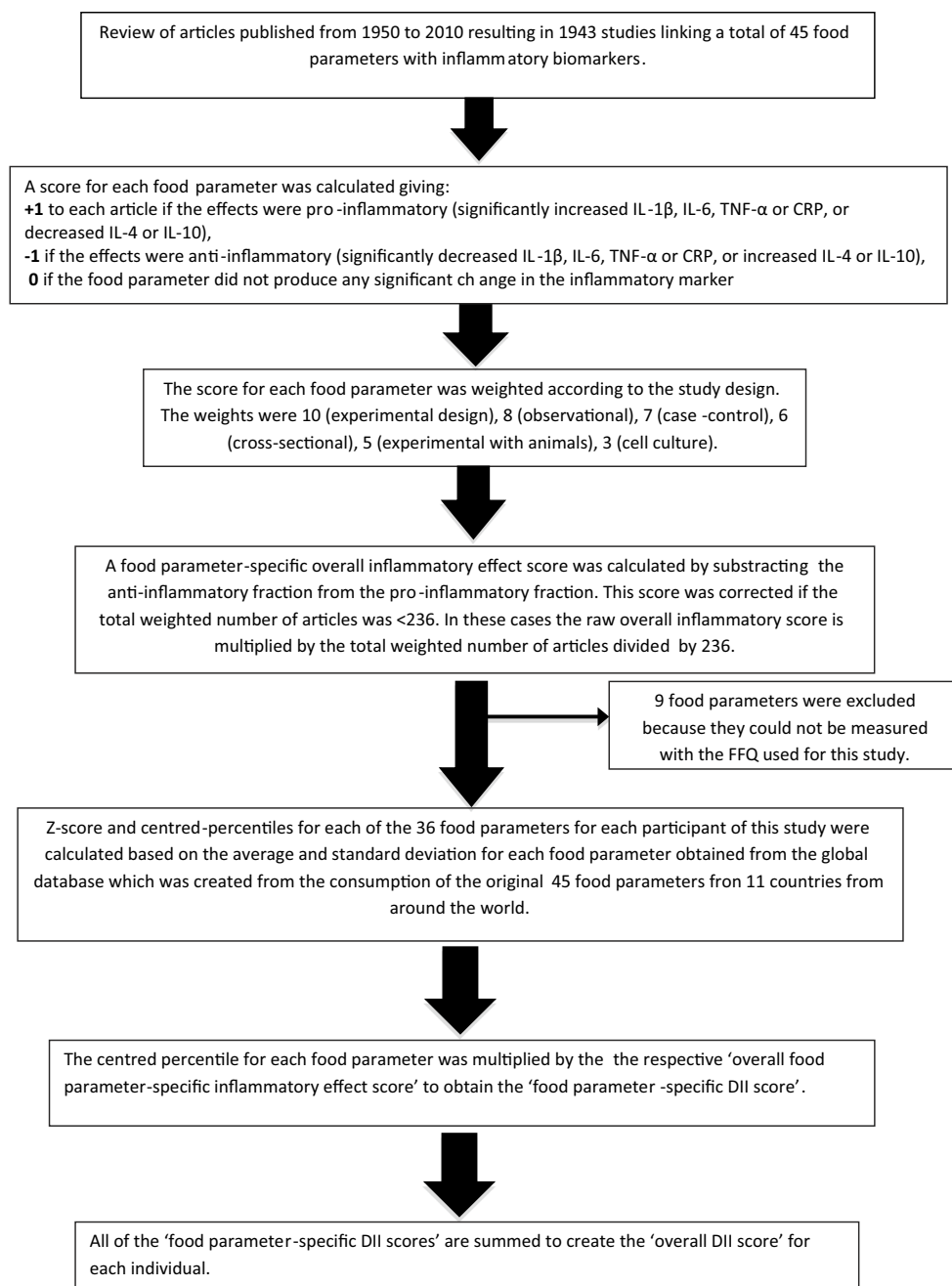
Fig. 1 Sequence of steps in creating the dietary inflammatory index in the Swedish oesophageal cancer case–control study

the included participants. Because the results were similar (results without exclusion are not shown), we report only results obtained after exclusion. Thus, data from a total of 181 cases of oesophageal adenocarcinoma, 255 cases of gastroesophageal junctional adenocarcinoma, 158 cases of oesophageal squamous cell carcinoma, and 806 control subjects remained for the final analysis. SAS® Statistical Package (version 9.0, SAS Institute Inc., Cary, NC) was used for all the analyses. All tests were two-sided with the significance level (α) set at 0.05.

Results

Study participants

The basic characteristics of all case patients compared to the control subjects are presented in Table 1. There were no significant differences between cases and control according to age, sex, and physical activity. However, on average, cases had higher BMI, higher energy intake,

Table 1 Distribution of the basic characteristics of oesophageal cancer cases and controls by quartiles of the dietary inflammation index (DII)

Variables[1]	Quartile of the dietary inflammatory index (DII)								p value[2]
	Controls (n = 806)				Cases (n = 594)				
	1 (<−1.04)	2 (−1.04–0.14)	3 (0.14–1.46)	4 (≥1.46)	1 (<−1.04)	2 (−1.04–0.14)	3 (0.14–1.46)	4 (≥1.46)	
No. of participants	202	201	201	202	107	135	139	213	
Age, years [mean (SD)]	64.5 (10.4)	65.6 (10.2)	67.1 (9.6)	66.6 (9.5)	64.6 (9.8)	64.5 (9.6)	64.5 (9.1)	67.1 (9.1)	0.32
Sex									0.77
Male	159 (23.8)	169 (25.4)	175 (26.2)	164 (24.6)	92 (18.9)	112 (23.0)	122 (25.0)	162 (33.1)	
Female	43 (30.9)	32 (23.1)	26 (18.7)	38 (27.3)	15 (14.2)	23 (21.7)	17 (16.0)	51 (48.1)	
Body mass index (BMI, kg/m²)									<0.0001
<25	153 (27.2)	133 (23.7)	136 (24.2)	140 (24.9)	63 (19.4)	70 (21.5)	70 (21.5)	122 (37.5)	
25.0–29.9	41 (19.1)	61 (28.3)	60 (27.9)	53 (24.7)	36 (16.8)	49 (22.9)	57 (26.6)	72 (33.7)	
≥30.0	8 (32.0)	6 (24.0)	5 (20.0)	6 (24.0)	8 (14.6)	16 (29.0)	12 (21.8)	19 (34.6)	
Education (years)									0.0007
≤9	85 (17.4)	114 (23.3)	147 (30.1)	143 (29.2)	58 (13.9)	89 (21.4)	103 (24.8)	166 (39.9)	
10–12	42 (26.6)	43 (27.2)	36 (22.8)	37 (23.4)	26 (26.3)	25 (25.3)	19 (19.1)	29 (29.3)	
≥13	75 (47.2)	44 (27.7)	18 (11.3)	22 (13.8)	23 (29.1)	21 (26.6)	17 (21.5)	18 (22.8)	
Reflux									<0.0001
Yes	41 (31.3)	27 (20.6)	42 (32.1)	21 (16.0)	42 (20.1)	50 (23.9)	47 (22.5)	70 (32.5)	
No	161 (23.9)	174 (25.8)	159 (23.5)	181 (26.8)	65 (16.9)	85 (22.1)	92 (23.9)	143 (37.1)	
Smoking status									<0.0001
Never	80 (24.9)	94 (29.3)	81 (25.2)	66 (20.6)	20 (17.1)	29 (24.8)	23 (19.6)	45 (38.5)	
Ever	76 (24.7)	72 (23.3)	80 (25.9)	81 (26.1)	43 (17.4)	56 (22.7)	63 (25.5)	85 (34.4)	
Current	46 (26.1)	35 (19.9)	40 (22.7)	55 (31.3)	44 (19.1)	50 (21.7)	53 (23.1)	83 (36.1)	
Alcohol (g/week, median)	39.0	24.3	19.0	11.0	69.6	35.5	29.0	13.0	<0.0001
Physical activity									0.36
1—low	41 (27.9)	34 (19.0)	38 (21.2)	66 (36.9)	17 (12.7)	28 (20.9)	26 (19.4)	63 (47.0)	
2	65 (25.4)	66 (25.8)	71 (27.7)	54 (21.1)	31 (17.3)	38 (21.2)	43 (24.1)	67 (37.4)	
3	51 (23.5)	54 (24.9)	59 (27.2)	53 (24.4)	28 (19.2)	37 (25.3)	29 (19.9)	52 (35.6)	
4—high	45 (29.2)	47 (30.5)	33 (21.4)	29 (18.9)	31 (23.0)	32 (23.7)	41 (30.3)	31 (23.0)	
Energy (kcal/day, median)	2268.9	2191.3	2145.7	1732.0	2564.9	2224.9	2221.7	1787.1	0.02
Helicobacter pylori (HP) infection									<0.0001
HP+ and CagA+	42 (22.8)	42 (22.8)	47 (25.6)	53 (28.8)	17 (21.0)	15 (18.5)	22 (27.2)	27 (33.3)	
HP+ or CagA+	29 (25.2)	32 (27.8)	33 (28.7)	21 (18.3)	28 (28.0)	23 (23.0)	20 (20.0)	29 (29.0)	
HP− negative	50 (25.6)	59 (30.3)	41 (21.0)	45 (23.1)	17 (14.5)	31 (26.5)	22 (18.8)	47 (40.2)	

[1] For all categorical variables values shown are number (percentage)

[2] t test was used for comparison of continuous variables (age, energy, alcohol consumption) between cases and controls. Chi-square was used to compare the difference of categorical variables (body mass index, education, reflux, smoking status, physical activity, and Helicobacter pylori infection) between cases and controls

Table 2 Average intake of food (g/day) and its standard deviation (STD) based on quartiles of the dietary inflammation index (DII)

Food	Dietary inflammatory index quartile (DII)										p value[2]
	Controls					Cases					
	1 (<−1.04)	2 (−1.04–0.14)	3 (0.14–1.46)	4 (≥1.46)	p value[1] for trend	1 (<−1.04)	2 (−1.04–0.14)	3 (0.14–1.46)	4 (≥1.46)	p value[1] for trend	
No. of participants	202	201	201	202		107	135	139	213		
Fruit	189.8 (107.8)	164.4 (117.5)	123.9 (81.1)	87.8 (77.2)	<0.0001	187.3 (133.7)	146.8 (86.6)	119.0 (95.4)	84.6 (72.0)	<0.0001	0.004
Vegetables	150.1 (67.3)	94.9 (53.4)	70.0 (41.9)	49.1 (36.7)	<0.0001	122.4 (76.1)	84.8 (51.6)	67.5 (41.0)	46.0 (31.8)	<0.0001	<0.001
Tomato	33.5 (19.8)	23.0 (17.8)	18.7 (16.8)	12.4 (13.6)	<0.0001	33.0 (24.8)	25.2 (21.6)	20.5 (18.8)	11.2 (11.7)	<0.0001	0.20
Whole grain	280.7 (211.0)	269.1 (177.9)	294.8 (209.6)	213.6 (124.6)	0.003	289.4 (297.4)	267.1 (155.9)	256.0 (132.6)	197.7 (88.0)	<0.0001	0.03
Refined grain	87.6 (441.0)	64.4 (33.6)	56.7 (29.8)	45.3 (26.8)	<0.0001	81.7 (45.0)	64.5 (36.5)	54.0 (33.8)	43.0 (26.5)	<0.0001	0.002
Low-fat dairy	372.4 (415.3)	523.6 (427.2)	597.1 (383.5)	532.4 (390.8)	<0.0001	482.8 (460.4)	593.4 (652.4)	682.4 (431.2)	543.8 (384.8)	0.41	0.003
High-fat dairy	146.7 (97.9)	146.4 (113.3)	126.8 (162.3)	98.3 (80.9)	<0.0001	156.0 (110.0)	143.0 (248.9)	138.8 (191.8)	89.6 (78.6)	0.0002	0.57
Fish	28.1 (21.8)	20.3 (11.1)	19.0 (10.2)	15.4 (8.3)	<0.0001	27.5 (17.8)	20.4 (13.3)	22.7 (23.9)	15.6 (8.5)	<0.0001	0.81
Chicken	11.4 (7.5)	8.0 (6.2)	7.3 (10.3)	5.7 (4.8)	<0.0001	11.8 (13.9)	9.1 (8.1)	7.8 (6.6)	5.9 (5.3)	<0.0001	0.94
Red meat	79.4 (38.6)	73.2 (31.2)	76.2 (36.3)	59.2 (22.2)	<0.0001	96.2 (78.6)	76.4 (31.6)	80.0 (34.9)	62.1 (26.7)	<0.0001	0.08
Processed meat	68.2 (44.0)	75.6 (44.4)	79.8 (46.8)	65.5 (31.0)	0.78	76.8 (45.2)	81.2 (38.6)	81.1 (46.3)	71.1 (35.3)	0.10	0.05
Eggs	21.5 (21.4)	20.8 (33.1)	18.4 (15.7)	15.2 (13.9)	<0.0001	27.0 (22.7)	25.5 (22.2)	22.1 (19.6)	15.3 (13.9)	<0.0001	0.04
Potatoes	176.1 (130.0)	176.7 (98.2)	171.1 (59.0)	155.4 (46.3)	0.0002	189.6 (139.1)	180.0 (56.2)	186.9 (66.1)	160.0 (50.0)	0.001	0.17
Sweets	43.2 (32.0)	49.4 (32.6)	50.5 (34.1)	42.6 (29.4)	0.94	53.5 (37.7)	55.1 (49.4)	51.1 (32.9)	44.2 (32.9)	0.01	0.06
Juice	94.6 (104.8)	44.2 (76.5)	26.1 (49.5)	19.2 (39.6)	<0.0001	100.6 (123.1)	50.4 (79.2)	26.6 (63.2)	18.0 (46.9)	<0.0001	0.36
High-energy drink	185.6 (249.2)	195.1 (250.7)	207.6 (313.0)	163.8 (227.2)	0.52	312.1 (530.8)	210.3 (223.7)	202.6 (280.0)	153.3 (198.0)	<0.0001	0.23
Nuts	1.5 (3,4)	0.9 (2.6)	0.7 (2.0)	0.3 (0.6)	<0.0001	2.8 (5.7)	1.3 (4.1)	0.6 (1.1)	0.3 (0.7)	<0.0001	0.21
Tea	339.6 (339.0)	221.2 (303.8)	69.6 (145.6)	5.1 (18.1)	<0.0001	338.1 (383.5)	148.1 (204.0)	42.7 (102.8)	4.1 (13.4)	<0.0001	0.0001
Coffee	687.6 (533.3)	663.9 (494.7)	790.6 (526.8)	806.5 (439.8)	0.002	734.8 (551.4)	807.8 (483.3)	872.4 (541.5)	820.8 (432.8)	0.15	0.004
Beer	508.5 (853.3)	354.9 (581.3)	294.2 (342.8)	228.3 (271.0)	<0.0001	854.0 (1481.5)	566.9 (1089.7)	580.0 (1222.6)	254.7 (338.3)	<0.0001	0.0009
Wine	98.5 (459.3)	27.9 (40.3)	25.8 (43.0)	22.7 (31.8)	0.02	105.0 (143.6)	43.9 (55.3)	39.4 (91.7)	18.9 (31.3)	<0.0001	0.95
Liquor	15.5 (23.1)	13.5 (19.9)	23.8 (77.2)	12.5 (20.2)	0.91	67.1 (213.3)	38.8 (96.3)	33.9 (56.7)	19.7 (33.5)	0.002	<0.0001

[1] p value for trend was computed based on correlation analysis between intake of specific food and the dietary inflammation index (DII)

[2] p value to compare the differences among control and case groups

Table 3 Odds ratios (ORs) and 95 % CIs for oesophageal cancer in relation to the dietary inflammation index (DII)

Models[1]	Total	Dietary inflammatory index quartile (DII)				p for trend[4]
		1 (<−1.04)	2 (−1.04–0.14)	3 (0.14–1.46)	4 (≥1.46)	
Controls number (%)	806	202 (25.1)	201 (24.9)	201 (24.9)	202 (25.1)	
Oesophageal squamous cell carcinoma						
No. (%)	158	25 (15.8)	39 (24.7)	32 (20.3)	62 (39.2)	
Age- and sex-adjusted OR		Referent	1.63 (0.94, 2.82)	1.37 (0.78, 2.42)	2.55 (1.53, 4.27)	0.0008
Multivariable-adjusted OR[2]		Referent	2.67 (1.44, 4.95)	1.69 (0.89, 3.22)	4.35 (2.24, 8.43)	0.0001
Oesophageal adenocarcinoma						
No. (%)	181	29 (16.0)	43 (23.8)	43 (23.8)	66 (36.4)	
Age- and sex-adjusted OR		Referent	1.48 (0.89, 2.46)	1.44 (0.86, 2.41)	2.25 (1.39, 3.64)	0.001
Multivariable-adjusted OR[3]		Referent	1.92 (1.06, 3.47)	1.57 (0.85, 2.89)	3.59 (1.87, 6.89)	0.0001
Gastroesophageal junctional adenocarcinoma						
No. (%)	255	53 (20.8)	53 (20.8)	64 (25.1)	85 (33.3)	
Age- and sex-adjusted OR		Referent	1.02 (0.66, 1.57)	1.25 (0.82, 1.90)	1.66 (1.11, 2.47)	0.007
Multivariable-adjusted OR[3]		Referent	1.22 (0.77, 1.94)	1.32 (0.83, 2.09)	2.04 (1.24, 3.36)	0.0001
Oesophageal or gastroesophageal junction adenocarcinoma						
No. (%)	436	82 (18.8)	96 (22.1)	107 (24.5)	151 (34.6)	
Age- and sex-adjusted OR		Referent	1.18 (0.83, 1.68)	1.31 (0.93, 1.87)	1.88 (1.35, 2.63)	0.0002
Multivariable-adjusted OR[3]		Referent	1.37 (0.92, 2.03)	1.36 (0.91, 2.03)	2.42 (1.57, 3.73)	<0.0001

[1] Odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated based on unconditional logistic regression

[2] Adjusted for age, sex, energy, education, tobacco smoking, alcohol intake, and physical activity

[3] Adjusted for age, sex, energy, education, tobacco smoking, alcohol intake, physical activity, reflux, and *Helicobacter pylori* infection

[4] Two-sided *p* values for trend were calculated using the Wald statistics, using the DII score as a continuous variable

more reflux, drank more alcohol, tended to be smokers, and had lower education (Table 1). A highly significant reduction in the consumption of anti-inflammatory dietary components such as fruits, vegetables, and fish was shown across DII quartiles (all *p* values <0.01), while this was not seen in pro-inflammatory components such as processed meat, sweets, and high-energy drinks (*p* values >0.50).

DII scores by food groups

The average intake of food groups by quartiles of DII scores is shown in Table 2. Some food types, e.g. fruit, vegetables, tomatoes, whole grain, tea, and juice, decreased across quartiles of DII scores (i.e. indicating increased inflammation). A similar gradient of food intake was evident in tertile or quintile classification of DII scores in both cases and controls (data not shown), indicating that the relationship between the DII scores and the foods comprising it was relatively invariant according to how the DII exposure was categorised. This indicates that the same foods tended to contribute to DII scores in the entire population, but is uninformative with respect to the relationship between DII scores and risk of oesophageal cancer.

DII scores and risk of oesophageal squamous cell carcinoma

As given in Table 3, based on the multivariable model, participants in the fourth quartile of DII scores had more than four times higher risk of oesophageal squamous cell carcinoma than participants in the first quartile (OR 4.35, 95 % CI 2.24, 8.43). A significant trend was observed across the quartiles (Table 3). In the BMI < 25 kg/m^2 group, a positive association remained when the highest quartile was compared with the lowest quartile. In the BMI ≥ 25 kg/m^2 group, an OR of 6.60 was observed (95 % CI 1.92, 22.70), although the reference group had only eight cases of oesophageal squamous cell carcinoma and the confidence interval was, therefore, wide (Table 4).

DII scores and risk of oesophageal and junctional adenocarcinoma

There were positive associations between DII scores (all comparing the fourth to the first quartile) and a risk of oesophageal adenocarcinoma (OR 3.59, 95 % CI 1.87, 6.89) and gastroesophageal junctional adenocarcinoma (OR 2.04, 95 % CI 1.24, 3.36) and for these tumours combined (2.42, 95 %CI 1.57, 3.73). All *p* values for linear trend were

Table 4 Odds ratios (ORs) and 95 % CIs for squamous cell and adenocarcinoma of the oesophagus and gastroesophageal junction in relation to the DII, stratified by BMI subgroups

Models[1]	Total	DII score (continuous)	Dietary inflammatory index quartile (DII)				p value for trend[3]	p value for interaction[4]
			1 (<−1.04)	2 (−1.04–0.14)	3 (0.14–1.46)	4 (≥1.46)		
Oesophageal squamous cell cancer[2]								
BMI <25 kg/m²								
No. (%)	107		17 (15.9)	27 (25.2)	23 (21.5)	40 (37.4)		
OR (95 % CI)		1.26 (1.09–1.46)	Referent	2.99 (1.40, 6.42)	1.73 (0.78, 3.81)	3.97 (1.74, 9.04)	0.004	
BMI ≥ 25 kg/m²								
No. (%)	51		8 (15.7)	12 (23.53)	9 (17.7)	22 (43.1)		
OR (95 % CI)		1.37 (1.09–1.73)	Referent	2.07 (0.66, 6.53)	1.75 (0.53, 5.75)	6.60 (1.92, 22.70)	0.006	0.03
Oesophageal adenocarcinoma[3]								
BMI <25 kg/m²								
No. (%)	76		13 (17.1)	18 (23.7)	18 (23.7)	27 (35.5)		
OR (95 % CI)		1.30 (1.08–1.56)	Referent	2.77 (1.13, 6.78)	2.32 (0.91, 5.87)	4.60 (1.71, 12.37)	0.006	
BMI ≥ 25 kg/m²								
No. (%)	105		16 (15.2)	25 (23.8)	25 (23.8)	39 (37.1)		
OR (95 % CI)		1.28 (1.07–1.54)	Referent	1.10 (0.45, 2.70)	0.98 (0.39, 2.46)	3.45 (1.26, 9.41)	0.004	<0.0001
Gastroesophageal junctional adenocarcinoma[3]								
BMI <25 kg/m²								
No. (%)	142		33 (23.2)	25 (17.6)	29 (20.4)	55 (38.7)		
OR (95 % CI)		1.15 (1.01–1.31)	Referent	0.98 (0.53, 1.83)	0.96 (0.52, 1.77)	1.66 (0.89, 3.13)	0.04	
BMI ≥ 25 kg/m²								
No. (%)	113		20 (17.7)	28 (24.8)	35 (31.0)	30 (26.6)		
OR (95 % CI)		1.22 (1.03–1.44)	Referent	1.30 (0.59, 2.87)	1.54 (0.69, 3.44)	2.90 (1.13, 7.46)	0.05	<0.0001
Oesophageal or gastroesophageal junction adenocarcinoma[3]								
BMI <25 kg/m²								
No. (%)	218		46 (21.1)	43 (19.7)	47 (21.6)	82 (37.6)		
OR (95 % CI)		1.15 (1.01–1.31)	Referent	1.32 (0.78, 2.23)	1.23 (0.72, 2.09)	2.21 (1.26, 3.86)	0.003	
BMI ≥ 25 kg/m²								
No. (%)	218		36 (16.5)	53 (24.3)	60 (27.5)	69 (31.7)		
OR (95 % CI)		1.23 (1.07–1.42)	Referent	1.13 (0.58, 2.19)	1.23 (0.62, 2.42)	2.98 (1.39, 6.41)	0.004	<0.0001

[1] Odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated using logistic regression

[2] Adjusted for age, sex, energy, education, tobacco smoking, alcohol intake, physical activity, reflux, and *Helicobacter pylori* infection

[3] Two-sided p values for trend across quartile of DII were calculated using the Wald statistics, using the DII score as a continuous variable

[4] Two-sided p values for interaction across quartile of DII were calculated based on the interaction item of body mass index (BMI) and the dietary inflammatory index (DII)

statistically significant (Table 3). In the subanalysis stratified by BMI, a persistently increased risk was observed for oesophageal adenocarcinomas in normal and lean body weight individuals (BMI < 25 kg/m^2), but not for gastro-adenocarcinomas of the oesophageal junction (Table 4). In individuals who were overweight or obese (BMI ≥ 25 kg/m^2), results similar to the general model (Table 3) were observed (Table 4).

Discussion

Results from the current study suggest that diet-related inflammation is associated with oesophageal cancers of both main histological types. A higher intake of relevant food, e.g. plant-based food, fish, tea, may constitute the major cause of diet-related anti-inflammation.

An association between diet and inflammation has been consistently demonstrated in observational studies [21], intervention trials [22, 23], and animal experiments [24]. In these studies, low-fat diet [22], fruit [25], tomatoes [23, 26], nuts [27], whole grains [21, 28], fish [29], and, especially, nutrients from foods rich in phytochemicals or antioxidants (e.g. carotene, lycopene, vitamin C, flavonoids [30–32]) have been found to have anti-inflammatory properties. In contrast, high-fat foods (e.g. sausage, cookies, biscuits, cake, pastries) [33], high-energy (e.g. sugar-sweetened) drinks [34, 35], and processed meat [36, 37] have been associated with pro-inflammatory properties. The results of diet analyses based on DII scores in the present study are consistent with those of previous studies addressing other cancer outcomes [38–40]. However, to the best of our knowledge, this study is the first to examine inflammation as regards whole diet and risk of oesophageal cancer.

Recent studies have shown oesophageal adenocarcinoma to be a good model for an inflammation-associated cancer [3]. The emerging consensus is that multiple pro-inflammatory pathways, fuelled by gastroesophageal reflux, Barrett's oesophagus, obesity, and diet, are important to the pathogenesis of adenocarcinoma of the oesophagus and gastro-esophageal junction. Moreover, smoking tobacco seems to cause a strong inflammatory reaction with an increased release of potentially tissue-destructive substances including pro-inflammatory cytokines that may contribute to the development of oesophageal cancer, especially squamous cell carcinoma of the oesophagus [41]. Diet may play pro- or anti-inflammatory roles depending on the type of food, processing methods, or the intermediary mechanism between diet and obesity (over nutrition, malnutrition, etc.). Pro-inflammatory characteristics of food/nutrients have been associated with an increased risk of oesophageal cancer. Zinc deficiency, for example, has been found to activate

inflammation with upregulation of numerous cancer-related inflammation genes, thus promoting murine oral oesophageal tumour progression [8, 42]. A higher intake of carbohydrates from higher glycaemic index food sources was associated with circulating concentrations of pro- and anti-inflammatory immune mediators. These, in turn, have been associated with oesophageal carcinogenesis [21, 43, 44]. In contrast, accumulating evidence has shown that some food types are protective against cancer, including oesophageal cancer, through their anti-inflammatory effects; e.g. soy protein inhibits inflammation by inhibiting the NF-κB and AKT signalling pathway [45], cocoa polyphenols prevent inflammation in the colon [46], olive oil and omega-3 fatty acids possess anti-inflammatory effects [47]. Increased risk by BMI may reflect the potential modulation of inflammation between diet, body composition, and oesophageal cancer. It must be cautioned, however, that the results might be due to chance because of relatively small numbers in BMI subcategories. The consistently higher ORs with increases in DII scores in the group with lower BMI indicate diet-related inflammation exists in this group as well. This finding is consistent with some previous studies regarding higher leptin or lower adiponectin levels among individuals with abdominal obesity in lean, compared with heavier, subjects [48–50].

The pro- or anti-inflammation properties of food/nutrients are considered promising for diet-based prevention or chemoprevention of oesophageal cancer. Phytochemicals in the diet, e.g. honokiol, a polyphenol in herbal tea, has been shown to increase necrosis and apoptosis in Barrett's cells through inhibiting the inflammatory reaction and to exhibit a similar effect on oesophageal adenocarcinoma cells [51]. Resveratrol, which is rich in grapes, was found to be a natural COX-2 inhibitor that is involved in the anti-inflammatory pathway [52]. Another phytochemical, curcumin, which can downregulate inflammation, was demonstrated to be capable of abolishing the ability of deoxycholic acid to activate NF-κB [53]. Omega-3 fatty acids, which are abundant in fish and have been associated with a protective effect concerning oesophageal cancer, can stimulate anti-inflammatory signalling molecules [54].

The strengths of this study include its population-based design with high participation rates and a large number of thoroughly classified oesophageal cancer cases. Moreover, the adjustment for all established aetiologic factors was a major strength of the study. This is one of only a few case–control studies that collected data on all the main types of oesophageal cancer, thus enabling us to assess associations for the different subtypes. The study participants were unaware of the hypothesis; hence, the risk of information bias is minimised. The validated questionnaire, collection of blood samples, and complete ascertainment of cases ensured the quality of the study and validity of the results.

Despite its strengths, the study does have potential weaknesses. A differential recall bias resulting from case–control study design is a potential source of error. The food frequency questionnaire is a tool that is used for reasons of expediency in large-scale epidemiologic studies, despite the fact that it is associated with method-specific errors, which might be influenced by response set and memory bias, sex, and education [55]. There is the potential problem of recent diet be influenced by disease status, which, in turn, could result in disease-differential reporting bias. Therefore, we asked participants to recall dietary habits 20 years before the interviews, which may reduce such a bias. However, asking respondents to recall dietary intake from so far in the past may exacerbate problems with memory and biased recall. Also, the small number of individuals in the BMI-stratified analysis produces results that might be somewhat unstable. However, results based on the main analysis appeared to be reliable. Another practical limitation, common to such observational studies, is that information on dietary supplements cannot be used for calculating the DII due to too many missing data on supplement use. Although this might not be a limitation *per se*, it should be noted that compared to most other diet indices, e.g. Health Eating Index (HEI), Alternative Health Eating Index (A-HEI), DASH (Dietary Approaches to Stop Hypertension), MED (Mediterranean diet), the DII is computed using a complicated set of algorithms. Technically, the DII can be calculated without collaborating with its inventors because the method is well described in a published paper [15]. However, given the complicated process of scoring and the various complexities involved in interpreting results, potential collaborations with the inventor are encouraged and virtually all requests are honoured.

This study suggests that diet-related inflammation may contribute to the aetiology of oesophageal cancer regardless of histological type. These results will have to be reproduced in other studies (including prospective cohorts) to confirm any causal association between diet-related inflammation and oesophageal cancer.

Compliance with Ethical Standards

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