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ANTIOXIDANTS AND CANCERS OF THE ESOPHAGUS AND GASTRIC CARDIA

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Antioxidant vitamins have attracted considerable attention in previous studies of esophageal squamous-cell carcinoma, but dietary studies of adenocarcinoma of the esophagus and gastric cardia remain sparse. Treating these tumors as distinct diseases, we studied intakes of vitamin C, beta-carotene and alpha-tocopherol in a nationwide population-based case-control study in Sweden, with 185, 165, and 258 cases of esophageal adenocarcinoma, esophageal squamous-cell carcinoma, and gastric cardia adenocarcinoma, respectively, and 815 controls. Subjects with a high parallel intake of vitamin C, beta-carotene, and alpha-tocopherol showed a 40–50% decreased risk of both histological types of esophageal cancer compared with subjects with a low parallel intake. Antioxidant intake was not associated with the risk of gastric cardia adenocarcinoma. Separately, vitamin C and beta-carotene reduced the risk of esophageal cancers more than alpha-tocopherol. We found that antioxidant intake is associated with similar risk reductions for both main histological types of esophageal cancer. Our findings indicate that antioxidants do not explain the diverging incidence rates of the 2 histological types of esophageal cancer. Moreover, our data suggest that inverse associations with esophageal squamous-cell carcinoma and adenocarcinoma may be stronger among subjects under presumed higher oxidative stress due to smoking or gastroesophageal reflux, respectively. Our results may be relevant for the implementation of focused, cost-effective preventive measures. ***Int. J. Cancer*** **87:750–754, 2000.**
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Overall rates of esophageal cancer remain higher in less-developed regions as compared with more-developed regions (IARC, 1998). The incidence of adenocarcinoma of the esophagus, however, which historically accounted for less than 10% of all esophageal cancer cases, has increased dramatically in Western populations over the last decades (Blot *et al.*, 1991), while the incidence of squamous-cell carcinoma of the esophagus has remained essentially stable (Thomas and Sobin, 1995). Although more uncertain due to the possibility of tumor misclassification (Ekstrom *et al.*, 1999), rates of adenocarcinoma of the gastroesophageal junction (gastric cardia) seem to have increased moderately (Blot *et al.*, 1991). In addition to differences in incidence rates, differences in risk factor profiles (Lagergren *et al.*, 2000) suggest that these tumors are distinct diseases with distinct etiologies.

Since the primary function of the esophagus is to serve as a conduit for ingested food, the possible role of dietary factors has attracted considerable attention in previous etiologic research. Most of the available data, however, pertain to squamous-cell carcinoma (or unspecified esophageal cancer), while information about dietary risk factors for esophageal and cardia adenocarcinoma remains sparse (Cheng and Day, 1996). Moreover, adenocarcinomas of the esophagus and gastric cardia have never been examined as separate diseases within a single investigation of nutritional factors.

Antioxidants have the potential to neutralize the harmful effects of DNA-damaging free radicals, such as those produced by smoking (Shklar, 1998), and these nutrients have generally emerged as protective factors in previous studies of esophageal squamous-cell carcinoma and unspecified esophageal cancer (Cheng and Day, 1996). The role of antioxidants in the etiology of adenocarcinoma of the esophagus and gastric cardia is unclear. Only one previous study has examined esophageal squamous-cell carcinoma and adenocarcinoma separately, but analyses of antioxidants were limited to vitamin C only and the number of cases was low (Tzonou *et al.*, 1996).

We studied the effects of vitamin C, beta-carotene, and alpha-tocopherol in relation to the risk of adenocarcinoma of the esophagus, adenocarcinoma of the gastric cardia, and squamous-cell carcinoma of the esophagus in a nationwide population-based case-control study in Sweden. We further examined subgroups according to smoking and gastroesophageal reflux status to identify potential modification of the effects of antioxidant intake by these sources of oxidative stress.

MATERIAL AND METHODS

Subjects

The design of this study has been described in detail elsewhere (Lagergren *et al.*, 1999). In brief, during 1995 through 1997 all newly diagnosed patients with adenocarcinoma of the esophagus (216 cases) or gastric cardia (313 cases) and half of the patients with squamous-cell carcinoma of the esophagus (228 cases, born on even dates) in the entire Swedish population below 80 years of age were eligible. A comprehensive organization encompassing all relevant hospital departments in Sweden ensured that every case throughout the country was identified shortly after diagnosis. Cases were uniformly classified histologically and anatomically, and histological slides were reviewed by the study pathologist. Endoscopists, surgeons, and pathologists gave standardized, detailed descriptions of the location of the cancer in cases. For a case to be classified as a cancer of the gastric cardia, the tumor had to be an adenocarcinoma and to have its center within 2 cm proximal or 3 cm distal to the gastroesophageal junction. Control subjects were randomly selected from the computerized and continuously updated Swedish population register and frequency-matched to resemble the age and sex distribution among the adenocarcinoma cases.

Nonparticipation among cases (27/12.5% among patients with esophageal adenocarcinoma, 61/26.8% among those with squamous-cell carcinoma, and 51/16.3% among cardia cancer patients) was mainly (116/83.5%) attributed to poor clinical condition or death shortly after diagnosis. Nonparticipation among controls (308/27%) was most often (210/68.2%) due to unwillingness. Seven additional subjects were excluded from analysis because their total energy intakes were below or above 3 standard deviations from the mean, indicating errors in their responses to dietary questions. Further, 4 subjects were excluded due to missing information on body mass index and 3 subjects due to poor response regarding dietary questions. After all these exclusions, 185, 165, and 258 cases of adenocarcinoma of esophagus, squamous-cell carcinoma of the esophagus, and adenocarcinoma of the gastric cardia, respectively, and 815 controls remained for analysis.

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Dietary assessment and other exposures

All consenting subjects underwent computer-aided face-to-face interviews by specially trained, professional interviewers from Statistics Sweden**.** A structured food frequency questionnaire, a modified version of a previously evaluated questionnaire (Wolk *et al*., 1997), including 63 food and beverage items of interest, was used to evaluate dietary habits 20 years prior to interview. We asked about the usual frequency of consumption of each item. The respondent answered in terms of number of times per day, week, month, or year. Average daily intake for every food item was created for each subject by multiplying the frequency of consumption of specific food items by standard, item-specific portion sizes, based on the National Food Administration handbook (National Food Administration, 1988). Daily total energy and nutrient intakes were calculated using the Swedish food composition database (Bergström *et al*., 1991). Energy adjustment of nutrients was performed using the residual methodology recommended by Willett and Stampfer (1986). For ease of interpretation, we anti-logged residuals and adjusted all nutrients to 2,400 kcal, the round number closest to the mean energy intake in the study group. Values for antioxidants derived from supplements were added to energy-adjusted intake measures if the duration of supplement use was 3 years or longer. Based on the distribution among controls, quartiles of each nutrient were then created. We created an antioxidant index by summing the quartile scores for each of the 3 studied antioxidants.

Statistical analysis

Unconditional logistic regression was used in univariate and multivariate modeling. All multivariate models included age, sex, smoking, and body mass index, as these factors are potentially related to the studied cancers and to antioxidant intake. Model parameters were estimated by the maximum likelihood method (Breslow and Day, 1980). From these estimates, odds ratios with 95% confidence intervals (CI) were computed. Odds ratios estimated the relative risks of the three tumors studied. As a basis for the trend tests, scores were constructed from the categorized variables as successive integers. These scores were used in further analyses, and the results are presented as tests for trend. To evaluate potential effect modification by presence vs. absence of high levels of oxidative stress, we performed stratified analyses over categories of smoking and symptoms of gastroesophageal reflux.

RESULTS

Baseline characteristics of the study subjects are shown in Table I. The median age of the combined cases was 67 years, and for the controls the median age was 68. Males comprised 82% of the cases, with a higher percentage for adenocarcinomas and a lower percent for squamous-cell carcinoma of the esophagus. The proportion of subjects with a history of tobacco smoking was lowest among controls, greater among subjects with adenocarcinoma of the esophagus, even greater among subjects with cardia adenocarcinoma, and greatest among subjects with squamous-cell carcinoma of the esophagus. Median body mass index was lowest among the controls and among cases of squamous-cell carcinoma of the esophagus, and noticeably higher among cases with adenocarcinoma of the esophagus or gastric cardia. The prevalence of higher levels of alcohol drinking was markedly greater among cases with squamous-cell carcinoma and was slightly greater among cases of gastric cardia than among controls or cases of adenocarcinoma of the esophagus.

Separate effects of the studied antioxidants

The median total dietary intakes of the respective antioxidants were higher among controls than among cases for vitamin C and beta-carotene but not for alpha-tocopherol (Table I). Compared with controls, differences were less pronounced for gastric cardia cancer cases than for cases with esophageal adenocarcinoma or esophageal squamous-cell carcinoma. The prevalence of regular multivitamin supplement use for at least 3 years was 17.6% among cases and controls combined, with a slightly higher percentage among controls and the lowest proportion among cases with esophageal adenocarcinoma. Less than 2.5% of all subjects used vitamin C or alpha-tocopherol supplements regularly.

Relative risk estimates for each type of cancer across levels of antioxidant intake are presented in Table II. Vitamin C intake was inversely associated with the risk of both adenocarcinoma of the esophagus and squamous-cell carcinoma of the esophagus. Alpha-tocopherol intake was inversely associated with the risk of squamous-cell carcinoma, but no association was observed with either of the 2 adenocarcinoma types. Intake of beta-carotene showed an inverse association with the risk of both esophageal adenocarcinoma and squamous-cell carcinoma, with risk reductions of 40–50% in the highest quartile vs. the lowest. The dose-risk trend for beta-carotene was particularly evident for esophageal adenocarcinoma ($P = 0.0005$).

The Pearson correlations between total intakes of vitamin C and beta-carotene was $r = 0.43$, between vitamin C and alpha-tocopherol it was $r = 0.34$, and between beta-carotene and alpha-tocopherol it was $r = 0.23$. Mutual adjustment of these 3 antioxidants did not change results appreciably, although the strength and statistical significance of the inverse associations became slightly weaker for vitamin C and alpha-tocopherol. Additional adjustment for symptoms of gastroesophageal reflux did not significantly alter

TABLE I – BASELINE CHARACTERISTICS OF THE STUDY SUBJECTS

Factor	Adenocarcinoma of esophagus	Squamous-cell carcinoma of esophagus	Adenocarcinoma of gastric cardia	Controls
Number	185	165	258	815
Age (median in years)	69	67	66	68
Male (%)	162 (87.6)	118 (71.5)	219 (84.9)	675 (82.8)
Smoking (2 years before interview)				
Never (%)	56 (30.1)	22 (13.3)	43 (16.7)	323 (39.6)
Former (%)	86 (46.5)	44 (26.7)	124 (48.1)	313 (38.4)
Current (%)	43 (23.2)	99 (60.0)	91 (35.3)	179 (22.0)
Body mass index (median kg/m^2)	25.4	23.6	24.7	23.7
Alcohol (median g/day)	5.2	15.0	6.2	6.4
Total dietary intake (median)				
Total energy (kcal/day)	2,315	2,293	2,308	2,231
Vitamin C (mg/day)	47.8	47.3	49.1	51.3
Alpha-tocopherol (μg/day)	6.2	6.0	5.4	5.5
Beta-carotene (mg/day)	1.3	1.3	1.5	1.8
Supplement users for at least 3 years (%)				
Multivitamins	27 (14.6)	29 (17.6)	40 (15.5)	155 (19.0)
Vitamin C	3 (1.6)	2 (1.2)	6 (2.3)	11 (1.3)
Alpha-tocopherol	1 (0.5)	1 (0.6)	1 (0.4)	8 (1.0)

TABLE II – MULTIVARIATE-ADJUSTED ODDS RATIOS (95% CONFIDENCE INTERVALS) FOR TOTAL DIETARY ANTIOXIDANT INTAKE[1]

	Median intakes	Adenocarcinoma of the esophagus		Squamous-cell carcinoma of the esophagus		Adenocarcinoma of the gastric cardia	
		No. of cases	OR (95% CI)	No. of cases	OR (95% CI)	No. of cases	OR (95% CI)
Vitamin C (mg/day)							
Quartile 1	29	58	1.0 (referent)	57	1.0 (referent)	53	1.0 (referent)
Quartile 2	43	42	0.7 (0.4–1.1)	32	0.6 (0.4–0.9)	79	1.8 (1.1–2.2)
Quartile 3	58	43	0.7 (0.5–1.1)	40	0.7 (0.4–1.1)	63	1.4 (0.8–1.7)
Quartile 4	88	42	0.7 (0.4–1.1)	36	0.6 (0.4–1.0)	63	1.4 (1.0–2.7)
P for trend			0.15		0.06		0.26
Alpha-tocopherol (μg/day)							
Quartile 1	5.5	48	1.0 (referent)	54	1.0 (referent)	63	1.0 (referent)
Quartile 2	6.0	43	0.9 (0.7–1.6)	40	0.7 (0.4–1.1)	65	1.1 (0.7–1.6)
Quartile 3	6.3	50	1.0 (0.7–1.7)	34	0.7 (0.5–1.2)	66	1.2 (0.8–1.8)
Quartile 4	6.8	44	0.9 (0.5–1.6)	37	0.5 (0.2–1.0)	64	1.2 (0.8–1.7)
P for trend			0.80		0.09		0.38
Beta-carotene (mg/day)							
Quartile 1	0.7	62	1.0 (referent)	56	1.0 (referent)	70	1.0 (referent)
Quartile 2	1.4	69	1.1 (0.7–1.6)	49	0.8 (0.5–1.2)	88	1.3 (0.9–1.9)
Quartile 3	2.4	31	0.6 (0.4–0.9)	33	0.7 (0.4–1.2)	62	1.2 (0.8–1.8)
Quartile 4	5.0	23	0.5 (0.3–0.8)	27	0.6 (0.4–1.0)	38	0.8 (0.5–1.2)
P for trend			0.0005		0.05		0.44
Antioxidant index[2]							
Quartile 1		76	1.0 (referent)	65	1.0 (referent)	82	1.0 (referent)
Quartile 2		43	0.7 (0.5–1.1)	47	0.8 (0.5–1.3)	65	1.1 (0.8–1.6)
Quartile 3		40	0.7 (0.4–1.0)	26	0.6 (0.4–1.0)	62	1.3 (0.9–1.8)
Quartile 4		26	0.5 (0.3–0.9)	27	0.6 (0.4–1.1)	49	1.2 (0.8–1.8)
P for trend			0.009		0.04		0.24

[1]Multivariate models included age (5-year age groups), sex, body mass index (quartiles), and cigarette smoking (never, past, and current).–[2]Antioxidant index was created by summing the quartile scores of vitamin C, alpha-tocopherol, and beta-carotene.

the estimates for any of the specific antioxidants with any of the studied tumors, nor did additional adjustment for the effects of physical activity, education, alcohol consumption, or the amount and duration of tobacco use alter the results. None of the antioxidants were associated with a decreased risk of adenocarcinoma of the gastric cardia. In fact, as opposed to both types of esophageal cancer, there was a tendency toward positive associations between the occurrence of cardia cancer and previous antioxidant intake.

The combined effect of the studied antioxidants

Subjects with a high parallel intake of all 3 antioxidants were at decreased risk of both histological types of cancer of the esophagus but were not at decreased risk of cardia adenocarcinoma (Table II). Among subjects in the highest quartile of antioxidant index compared with the lowest, we observed a 50% reduction in risk ($P = 0.009$) for adenocarcinoma of the esophagus, and a 40% reduction in risk ($P = 0.04$) for squamous-cell carcinoma (Table II).

Vitamin supplement intake

There was practically no reduction in risk among the minority who had used vitamin supplements for 3 years or more. The odds ratios for any vitamin tablet use were 0.9 for adenocarcinoma of the esophagus and 1.0 for squamous-cell carcinoma of the esoph-

TABLE III – ODDS RATIOS FOR ESOPHAGEAL CANCER IN RELATION TO TOTAL DIETARY ANTIOXIDANTS AND ESOPHAGEAL CANCERS STRATIFIED BY TOBACCO SMOKING AND SYMPTOMS OF REFLUX[1]

		Squamous-cell carcinoma of the esophagus			Adenocarcinoma of the esophagus	
		Never smoker	Ex-smoker	Current smoker	No reflux	Reflux symptoms
Number of cases		22	44	99	74	111
Vitamin C (mg/day)						
Tertile 1	31.7	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Tertile 2	49.8	0.9	0.8	0.5[2]	1.1	0.6
Tertile 3	80.0	1.0	0.6	0.6	0.8	0.9
P for trend		0.99	0.44	0.07	0.46	0.62
Alpha-tocopherol (μg/day)						
Tertile 1	5.2	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Tertile 2	6.2	1.3	0.3[2]	0.8	1.7	1.2
Tertile 3	7.3	1.2	0.8	0.7	1.0	1.0
P for trend		0.82	0.53	0.20	0.94	0.99
Beta-carotene (mg/day)						
Tertile 1	0.8	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Tertile 2	1.5	0.5	0.6	0.7	1.5	0.4[3]
Tertile 3	3.6	0.8	0.5	0.6	0.8	0.3[4]
P for trend		0.89	0.07	0.07	0.47	0.0004
Antioxidant index						
Tertile 1		1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Tertile 2		1.0	0.4	0.9[2]	0.7	0.6
Tertile 3		1.1	0.8	0.4[2]	0.9	0.4[3]
P for trend		0.82	0.45	0.03	0.58	0.006

[1]Multivariate models included age (5-year age groups), sex, body mass index (quartiles), and cigarette smoking (never, past, and current).–[2]$P < 0.05$.–[3]$P < 0.01$.–[4]$P < 0.001$.

agus. Similar results were observed with supplements for vitamin C and alpha-tocopherol, where all point estimates were between 0.9 and 1.0, with wide confidence intervals (data not shown). Excluding supplement users and analyzing dietary intake of antioxidants from foods only did not change our results presented in Table II.

Effect modification

We hypothesized that the inverse association between antioxidant intake and cancer risk would be more pronounced in subjects whose tissues are under greater oxidative stress, e.g., due to smoking or chronic esophageal inflammation from gastroesophageal reflux. We therefore repeated our analyses after stratification by smoking status and presence or absence of reflux symptoms (Table III). Indeed, the inverse association between antioxidant intake and the risk of esophageal squamous-cell carcinoma was stronger among current smokers than among nonsmokers, although formal tests of interaction by smoking were not statistically significant. We found no indication of effect modification by smoking on the relationship between antioxidant intake and the risk of adenocarcinomas of the esophagus or gastric cardia. Our data also provide support for effect modification by reflux on the association between antioxidants and the risk of esophageal adenocarcinoma, where dose-risk trends appeared to be stronger among those who had experienced symptoms of gastroesophageal reflux at least once per week for more than 1 year. This effect was confined to cases of esophageal adenocarcinoma. We found no indications of effect modification by body mass index or alcohol intake for any of the studied tumors (data not shown).

DISCUSSION

We observed that higher intakes of antioxidants were associated with similarly decreased risks of esophageal adenocarcinoma and esophageal squamous-cell carcinoma, but we found no association with the risk of cardia adenocarcinoma. Subjects who had the highest parallel intake of all 3 studied antioxidants—vitamin C, alpha-tocopherol, and beta-carotene—showed 40–50% decreased risk of both histological types of esophageal cancer compared with subjects with the lowest parallel intake.

Our data lend support to our a priori hypothesis that persons at increased risk of cancer presumably due to higher oxidative stress experience greater benefits from antioxidant intake. Our findings suggest that the inverse associations of antioxidants with squamous-cell carcinoma are stronger among current smokers than among never smokers. For the first time to our knowledge, we examined the possibility that the inverse associations with adenocarcinoma of the esophagus are stronger among sufferers of gastroesophageal reflux and, as with smoking, we found some support for this hypothesis. As with smoking, reflux is likely to be associated with increased levels of DNA-damaging free radicals induced by chronic inflammation (Maeda and Akaike, 1998). Potential effect modification between vitamin C intake and smoking has similarly been shown in several previous studies (Barone *et al.*, 1992; Hu *et al.*, 1994; Tavani *et al.*, 1996) but not in all (Brown *et al.*, 1998). These observations seem to support the presumed antioxidative mechanisms by which these nutrients appear to confer protection (Nordmann, 1994; Shklar, 1998). In addition to deactivating excited oxygen molecules, vitamin C, beta-carotene, and alpha-tocopherol may also protect against carcinogenesis through other mechanisms, as has been discussed in a review of potential mechanisms related to these nutrients (Steinmetz and Potter, 1991).

Our findings are generally consistent with the findings of previous studies of antioxidants and esophageal cancers that considered histological type. Only one prior study, of smaller sample size, investigated separately both main histological types of esophageal cancer with respect to their relation to premorbid diet (Tzonou *et al.*, 1996). That study reported inverse associations between intake of vitamin C and risk of adenocarcinoma of the esophagus, although a nonsignificant reduction in risk was also observed for squamous-cell carcinoma. Another case-control study found inverse associations between vitamin C intake and the risk of squamous-cell carcinoma of the esophagus but not with the risk of combined adenocarcinomas of the esophagus and gastric cardia (Kabat *et al.*, 1993). Similarly, 2 case-control studies of adenocarcinomas of the esophagus and gastric cardia grouped together also showed no association with vitamin C intake (Brown *et al.*, 1995; Zhang *et al.*, 1997), although nonsignificant decreases in risk were observed in one of these studies with beta-carotene and vitamin E (alpha-tocopherol) (Zhang *et al.*, 1997). The lack of an association with the combined adenocarcinomas of the esophagus and gastric cardia in these previous studies confirms to some extent the lack of associations with adenocarcinoma of the gastric cardia in our data since the majority of cases in these studies were cardia cancers. Most previous investigations studying only squamous-cell carcinoma of the esophagus, or all esophageal cancers combined, generally show an inverse association with high intake of antioxidant vitamins C (Graham *et al.*, 1990; Tzonou *et al.*, 1996; Brown *et al.*, 1998; Launoy *et al.*, 1998). Studies of dietary beta-carotene or alpha-tocopherol in developed countries, by contrast, are few and the results have been inconsistent (Launoy *et al.*, 1998; Nomura *et al.*, 1997; Zheng *et al.*, 1995; Dorgan and Schatzkin, 1991).

A strength of our study is its population-based design. We identified practically all newly diagnosed cases of the 3 tumors in the study base and rigorously classified each according to histological type and site of the tumor. Our comparatively large study allowed separate analyses of the 3 studied tumors. To the best of our knowledge, ours is the first study to examine the 3 tumors separately within a single investigation of nutritional factors. A truly random sample from the entire study base acting as control subjects reduced the possibility that selection of control subjects was related to exposure. Our data were limited, however, by the strong likelihood of some degree of measurement error of the exposure, since questions pertained to dietary habits of 2 decades prior to interview (Wolk *et al.*, 1997). We chose to ask about dietary habits 20 years prior to interview in order to assess potential risk factors with a reasonable latency period before the occurrence of cancer. It should be noted that while questions regarding food intake pertained to 20 years prior to interview, our dietary questionnaire asked about vitamin use more broadly, up to 2 years prior to interview. Measurement error related to diet or dietary supplements would tend to weaken our findings, i.e., bias relative risk estimates toward unity (Rothman and Greenland, 1998). Hence, the inverse associations we observed for esophageal cancers would be stronger in the absence of measurement error in the 3 antioxidant intake estimates. Differential misclassification, i.e., recall bias, is possible in the retrospective assessment of exposure (Breslow and Day, 1980), although such nondifferential misclassification would be expected to bias our findings for cardia cancer toward a protective effect, which we did not observe. Finally, the antioxidants we studied may be correlated with other known or unknown anticarcinogens in foods, substances that theoretically might account for the major part of the seemingly protective effect.

In conclusion, we found that antioxidant intake, even in moderate amounts, is associated with lower risks of both main histological types of esophageal cancer. Thus, the diverging rates between histological types are likely not due to changing patterns of antioxidant intake. Our data suggest the possibility that the inverse associations are stronger among subjects under higher oxidative stress due to smoking or gastroesophageal reflux, which would also suggest that protection is conferred through an antioxidative mechanism. This insight may be relevant for the implementation of targeted, cost-effective preventive measures. The apparent lack of any association between antioxidants and the risk of adenocarcinoma of the gastric cardia suggests that this tumor may have etiological differences with cancers of the esophagus.

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