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Dietary antioxidants and risk of Barrett's esophagus and adenocarcinoma of the esophagus in an Australian population

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While dietary antioxidants are emerging as potentially modifiable risk factors for esophageal adenocarcinoma (EAC), studies on dietary antioxidants and its precursor Barrett's esophagus (BE) are limited. The present study extends previous work on BE by investigating risks of nondysplastic BE, dysplastic BE and EAC associated with intake of antioxidants such as vitamin C, vitamin

Key words: dietary antioxidants, antioxidant index score, nondysplastic Barrett's esophagus, dysplastic Barrett's esophagus, esophageal adenocarcinoma

Abbreviations: ACS: Australian Cancer Study; BE: Barrett's esophagus; EAC: esophageal adenocarcinoma; CI: confidence interval; FFQ: food frequency questionnaire; kJ: kilojoules; ORs: odds ratios; SDH: study of digestive health

Additional Supporting Information may be found in the online version of this article.

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E, β-carotene, and selenium. Age and sex matched control subjects (n=577 for BE; n=1,507 for EAC) were sampled from an Australian population register. Information on demography, and well established EAC risk factors were obtained using self-administered questionnaires. Intake of antioxidants for patients newly diagnosed with nondysplastic BE (n=266), dysplastic BE (n=101), or EAC (n=299), aged 18–79 years, were obtained using a food frequency questionnaire. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using multivariable adjusted logistic regression models. High intake of β-carotene from food and supplement sources combined was inversely associated with risk of dysplastic BE (OR Q4 *vs.* Q1=0.45; 95%CI: 0.20–1.00). High intake of vitamin E from food sources (OR Q4 *vs.* Q1=0.43; 95%CI: 0.28–0.67), from food and supplements combined (OR Q4 *vs.* Q1=0.64; 95%CI: 0.43–0.96), and a high antioxidant index score were inversely associated with risk of EAC. We found no significant trends between intake of β–carotene, vitamin C, vitamin E, and selenium and risk of nondysplastic or dysplastic BE. However, our data suggest that a high intake of β-carotene may be associated with decreased risk of dysplastic BE.

What's new?

Barrett's Esophagus (BE) is a premalignant condition caused by gastro-esophageal reflux that can progress to dysplasia and esophageal adenocarcinoma (EAC). The mechanisms behind this progression are unknown but oxidative stress has been implicated as a possible driver. The authors show that higher intake of beta-carotene is associated with reduced risk of dysplastic BE. A similar inverse association was observed for vitamin E consumption and EAC. In contrast, no association was observed between antioxidants and non-dysplastic BE. They point out that more research is necessary to understand how antioxidants protect the esophageal epithelium from malignant transformation.

Esophageal cancer is the eighth most common cancer, and the sixth most common cause of death from cancer world-wide.[1] Over the past four decades, the incidence of esophageal adenocarcinoma (EAC) has risen more rapidly in many high-income countries[2–5] including Australia.[6] EAC patients have a poor prognosis, with <20% surviving >5 years.[7] In the two decades prior to 2005, the annual percentage change in the incidence of EAC in men and women was 4.2 and 4.3%, respectively in New South Wales, Australia.[8] Similar increases have been reported in other Australian states[9] and internationally.[3]

Barrett's esophagus (BE), a known precursor lesion of EAC, is a premalignant condition in which the esophageal squamous epithelium is replaced by specialized intestinal metaplasia.[10] BE may progress to dysplasia and invasive adenocarcinoma although the factors that determine progression are not clear[11,12] and there is currently no way of predicting which BE patients will progress to EAC. It has been proposed that the sequence of events leading to cancer might be driven in part by oxidative and nitrosative stress.[13–15] In patients with BE, inflammation is caused by chronic gastroesophageal reflux, which results in the production of free radicals that promote carcinogenesis through DNA damage and inhibition of apoptosis.[16–18] Thus, antioxidant nutrients including vitamin C, vitamin E, β-carotene, and selenium might reduce the risk of precancerous as well as cancerous lesions by scavenging reactive oxygen species.

A recent review of the literature investigating the association between specific dietary components and risk of BE and cancers of the esophagus, reported inverse associations between increased intake of antioxidants, fruit, vegetables, and risk of EAC but the associations were not consistent across all studies.[19] Similarly, the results of the few studies[20–22] that have examined the association between dietary antioxidants and BE risk have also been inconsistent with some reporting significant inverse associations[20,21] while others found no association.[22] A limitation shared by previous studies on dietary antioxidants and BE is the failure to assess the effects of antioxidants on nondysplastic and dysplastic BE separately. Dysplasia precedes adenocarcinoma in BE; it arises from the metaplastic epithelium and has been proposed as a marker for detecting patients at high risk for developing carcinoma.[23]

Given the lack of information between antioxidant intake and risk of nondysplastic and dysplastic BE, the strong association between dysplastic BE and EAC, and increasing incidence of EAC in the Australian population and elsewhere, we have extended previous work in this area by evaluating the association between intake of dietary antioxidants and the risk of nondysplastic BE, dysplastic BE, and EAC.

Material and Methods

Study subjects

Data for these analyses came from two concurrent population-based studies: The Study of Digestive Health (SDH) and Australian Cancer Study (ACS). The SDH investigated environmental and genetic risk factors associated with Barrett's esophagus (BE) and a detailed description of the methods has been published previously.[24] In summary, eligible cases were people aged 18–79 years with a new diagnosis of histologically confirmed nondysplastic or dysplastic BE between 2003 and 2006. Barrett's esophagus was defined as the presence of specialized intestinal metaplasia (columnar epithelium with goblet cells) in a biopsy taken from the esophagus by upper gastrointestinal endoscopy, regardless of the length of

involvement.[25] Eligible patients were prospectively identified through the two major private pathology laboratories and a single public pathology laboratory serving metropolitan Brisbane (population 1.5 million) during the study period. Of all the patients approached, 487 were found to have a previous diagnosis of BE or a previous diagnosis of BE with dysplasia and were thus deemed ineligible for this study. We also excluded those who did not speak English (5) or who were too ill to participate (3). The final study group comprised 393 BE cases (285 nondysplastic and 108 dysplastic).

ACS investigated risk factors for cancers of the esophagus and a detailed description of the methods has been published previously.[26] Briefly, adult participants aged 18–79 years with a histologically confirmed primary EAC diagnosed between 2002 and 2005 were identified through major treatment centers throughout mainland Australia. Those missed at these centers were identified by state-based cancer registries (notification of cancer diagnosis is mandatory in all states of Australia). Details of the histological type and anatomical site of each tumor were abstracted from diagnostic pathology reports by medically qualified investigators. Tumor site was classified according to the WHO classification such that adenocarcinomas located entirely above the esophagogastric junction were considered esophageal carcinomas.[10] Of 1,102 patients (858 through clinics and 244 through cancer registries) who returned a completed questionnaire (70% of all invited), seven case patients were subsequently deemed ineligible on pathology review and were excluded from the analysis leaving 364 EAC cases. Participants with esophago-gastric junction adenocarcinoma (EGJAC) $n=425$ and esophageal squamous cell carcinoma (ESCC) $n=306$ were excluded from the present analyses.

Control participants, sampled from the same geographic regions as cases (*i.e.*, greater Brisbane area for SDH; mainland Australia for ACS), were randomly selected from the Australian Electoral Roll (enrolment is compulsory) and broadly matched to the case groups by age (in 5-year age groups), sex, and state of residence. Altogether, we collected data from 646 SDH controls (72% of eligible controls contacted) and 1,580 ACS controls (51% of eligible controls contacted).

All study participants provided informed written consent to take part. Both studies were approved by the human research ethics committee of the Queensland Institute of Medical Research and all participating institutions.

Nondietary data collection

We collected data from all participants via similar self-administered questionnaires. Information was collected on age, gender, education, as well as height and weight 1 year previously (1 year before diagnosis for cases). Participants were asked whether, over their whole life, they had ever smoked more than 100 cigarettes, cigars, or pipes; positive responses elicited further questions about ages started and stopped smoking and typical daily consumption. Pack-years of smoking were derived from duration and intensity of smoking. We assessed the frequency of symptoms of gastro-esophageal reflux defined as the presence of heartburn ("a burning pain behind the breastbone after eating") or acid reflux ("a sour taste from acid or bile rising up into the mouth or throat"), 10 years before diagnosis. Participants were also asked to report the frequency with which they consumed alcohol between ages 20–29, 30–49, and $\geq$50 years, as applicable. Total alcohol consumption was summed between age 20 years and current age. We obtained information on the use of nonsteroidal anti-inflammatory drugs in the past 5 years.

Dietary data collection

Dietary data were obtained using a 135-item semiquantitative food frequency questionnaire (FFQ). Participants were asked how often they consumed a specified amount of each food item in the previous year (for controls), or in the year before their diagnosis (for cases). Participants who reported that their diet had changed in the last 6–12 months were asked to report their usual diet before the change. The FFQ was modified from the instrument developed by Willett et al.[27] validated against weighed food records,[28–30] and serum carotenoid levels,[31] and found to be reproducible for use in Australia.[32] Reported frequencies were converted into intake in grams per day by multiplying the standard serving size of each food item as specified on the FFQ by the frequency of consumption per day. Dietary intake of beta-carotene, vitamins C, vitamin E, selenium and total energy was estimated using the 2007 electronic release version of the Australian food composition tables (NUTTAB 2006).[33] Among 100 control participants who completed a similar FFQ twice, 1 year apart, intra-class correlation coefficients obtained for the dietary antioxidants were: vitamin C=0.60, vitamin E=0.52, and β-carotene=0.68.[32] We corrected the nutrient intake for energy intake using the regression residual method described by Willett and Stampfer.[34] We also asked participants to report whether they regularly took multivitamin supplements in the previous year (for controls), or in the year before their diagnosis (for cases). If they did, the brand, type, strength, and number of tablets taken per week were queried. Information regarding ingredients in the multivitamins was obtained from the Australian Register of Therapeutic goods database as reported by product sponsors, and translated into a common unit for each nutrient following a process previously reported by Ashton et al.[35]

Exclusions and final sample size

After excluding participants who did not complete a FFQ, those who omitted responses to more than 10% of FFQ items, and those whose daily total energy was considered implausible (kJ <3,360 or >21,000 for men; and kJ <2,940 or >16,800 for women), the final dataset included 577 (89%) controls, 266 (93%) nondysplastic BE cases and 101 (93%) dysplastic BE cases for the Study of Digestive Health; and

1,507 (96%) controls, and 299 (82%) EAC cases 337 EGJAC, and 245 ESCC cases for the Australian Cancer Study.

Statistical analyses

Characteristics between cases and controls were compared using chi-squared statistics for categorical variables. We used unconditional multivariable-adjusted logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CI). Antioxidants (from food sources only), total antioxidants (from food and supplements combined), and fruit and vegetable intake were categorized using quartile cut-points of the distribution among control subjects. Quartile 1 served as the referent category for all regression analyses. To test for linear trends, categories of antioxidants were modeled as ordinal variables (with category values taking the median of the range). An antioxidant index, a measure of combined intake of β-carotene, vitamin C, vitamin E, and selenium, was calculated for each participant using the method described by Murphy et al.[22] Briefly, the antioxidant index summed the quartile category of β-carotene, vitamin C, vitamin E, and selenium intake for each participant. For example, a participant in the lowest quartile of intake for each of the four antioxidants had an antioxidant index equal to 4, while a participant in the highest category for each of the four antioxidants had an antioxidant index of 16. We estimated two antioxidant indices *viz*: antioxidant index (from food sources only) and total antioxidant index (from food and supplements combined). Because of intercorrelation of the nutrients, analyses were performed separately for each antioxidant. We simultaneously adjusted for the confounding effects of age (in years); gender; education (high school only, technical college or diploma); BMI 1 year previously ($<$25, 25–29.9, $\geq$30 kg m^{-2}); frequency of heartburn or acid reflux symptoms in the 10 years before diagnosis (never,$<$weekly,$\geq$weekly, daily); pack-years of smoking (0, 1–14.9, 15–29.9, $\geq$30); average lifetime alcohol intake (never, $<$1–6, 7–20, $\geq$21 standard drinks/week); use of nonsteroidal anti-inflammatory drugs in the past 5 years (never, occasionally,$<$weekly, $\geq$weekly); and total energy intake (kJ) log-transformed. Further adjustment for *H. pylori* seropositivity, use of proton pump inhibitors, use of hydrogen receptor antagonists, and physical activity did not alter effect estimates and these variables were not included in the final model.

To assess possible effect modification by risk factors such as alcohol, smoking, reflux and BMI, we tested for multiplicative interaction by including a product term between each antioxidant and risk factors (alcohol, smoking, reflux, and BMI) in a multivariable model. If statistically significant interactions were present, we stratified the analyses by the presence or absence of the risk factor. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC). All *P* values were two sided, and $P<0.05$ was considered statistically significant.

Results

Characteristics of cases and controls are presented in Table 1. On average, patients with dysplastic BE and EAC were slightly older and mostly males compared to nondysplastic cases and controls. As expected, all case groups were more likely to be obese ($\geq$30), heavy smokers ($\geq$30 pack years), have at least weekly reflux symptoms ($\geq$weekly), and consume more alcohol ($\geq$ 21 standard drinks/week) than controls. Except for β-carotene, mean intake of antioxidants was similar between BE cases and controls, but generally lower in EAC cases than controls (Table 1).

Results of the association between β-carotene, vitamin C, vitamin E, and selenium (from food sources only, and food and supplements combined) and risk of BE overall, is shown in Supporting Information Table 1. There were no associations between intake of the antioxidants and risk of BE overall after adjustment for confounders (Supporting Information Table 1).

Antioxidants from food sources only

We found no association between individual antioxidants or antioxidant index scores (from food sources only) and risk of nondysplastic or dysplastic BE, except for a significant positive association between higher intake of vitamin C and risk of nondysplastic BE (OR Q4 *vs.* Q1=1.90; 95%CI: 0.99–2.86; $P=0.05$) (Table 2). Higher intake of vitamin E (OR Q4 *vs.* Q1=0.43; 95%CI: 0.28, 0.67; $P=0.003$), and higher scores on the antioxidant index were inversely associated with risk of EAC (OR Q4 *vs.* Q1=0.49; 95%CI: 0.30, 0.80; $P=0.01$) (Table 2).

Antioxidants from food and supplements combined

The use of dietary supplements containing β-carotene (6%), selenium (6%), vitamin E (18%), and vitamin C (30%) is low in our study participants; thus, results are presented for antioxidants from food and supplements combined. We found a significant inverse association between intake of total β-carotene in the fourth quartile and risk of dysplastic BE (OR Q4 *vs.* Q1=0.45; 95%CI: 0.20–1.00). There were no significant trends associated with increasing intakes of total vitamin C, vitamin E, selenium, or total antioxidant index score and risk of nondysplastic or dysplastic BE however, intakes in the fourth quartile of the antioxidants were associated with lower risks of dysplastic BE than nondysplastic BE (Table 3). Higher intake of total vitamin E was associated with reduced risk of EAC (OR Q4 *vs.* Q1=0.64; 95%CI: 0.43, 0.96; $P=0.04$) (Table 3).

Fruit and vegetable intake

We found a positive association between high fruit intake and risk of nondysplastic BE (OR Q4 *vs.* Q1=1.83; 95%CI: 1.02, 3.29; $P=0.04$), and weak nonsignificant inverse associations between vegetable intake and risks of dysplastic BE and EAC (Table 4).

We further tested whether effect estimates (log odds) of dietary antioxidants at the same quartile level of intake differ between nondysplastic BE and dysplastic BE case groups using multinomial logistic regression, modeling the outcome

Table 1. Comparison of characteristics among cases and controls in study of digestive health and Australian cancer study participants

	Study of digestive health (SDH)					Australian cancer study (ACS)		
Characteristics	SDH controls (n=577)	Nondysplastic BE (n=266)	p value[1,2]	Dysplastic BE (n=101)	p value[1,3]	ACS controls (n=1,507)	EAC (n=299)	p value[1,4]
Age (y); mean ±SD	58 ±11	58±12	0.96	62±11	0.0008	61±12	64±10	<0.0001
Gender, n (%)			0.82		0.005			<0.0001
Female	208 (36.0)	98 (36.8)		22 (21.8)		511 (33.9)	28 (9.4)	
Male	369 (64.0)	168 (63.2)		79 (78.2)		996 (66.1)	271 (90.6)	
Educational qualification, n (%)			0.003		0.01			0.0002
School only	226 (39.2)	130 (48.9)		35 (34.5)		616 (40.9)	139 (46.5)	
Trade/diploma	224 (38.8)	101 (38.0)		54 (53.5)		657 (43.6)	141 (47.2)	
University	127 (22.0)	35 (13.1)		12 (11.9)		234 (15.5)	19 (6.4)	
Body mass index, n (%)			0.003		0.08			<0.0001
<25	211 (37.0)	76 (29.1)		27 (27.0)		541 (36.2)	60 (20.5)	
5–<30	235 (41.2)	105 (40.2)		47 (47.0)		642 (42.9)	125 (42.7)	
≥30	124 (21.8)	80 (30.7)		26 (26.0)		312 (20.9)	108 (36.9)	
Smoking history (pack years), n (%)			<0.0001		<0.0001			<0.0001
Never smoked	307 (53.2)	90 (33.8)		23 (22.8)		673 (44.7)	75 (25.1)	
<15	113 (19.6)	63 (23.7)		24 (23.4)		380 (25.2)	60 (20.1)	
15–29.9	67 (11.6)	54 (20.3)		27 (26.7)		199 (13.2)	57 (19.1)	
≥30	90 (15.6)	59 (22.2)		27 (26.7)		255 (16.9)	107 (35.8)	
Frequency of reflux symptoms 10 y ago, n (%)			<0.0001		<0.0001			<0.0001
Never	282 (48.9)	40 (15.2)		10 (10.0)		649 (43.1)	65 (21.8)	
occasionally	156 (27.0)	36 (13.6)		17 (17.0)		460 (30.5)	40 (13.4)	
<weekly	80 (13.9)	74 (28.0)		25 (25.0)		218 (14.5)	67 (22.5)	
≥weekly	59 (10.2)	114 (43.2)		48 (48.0)		180 (11.9)	126 (42.3)	
Mean alcohol consumption categories/week, n (%)[5]			0.63		0.63			<0.0001
Never	105 (18.2)	55 (20.8)		15 (15.0)		255 (16.9)	27 (9.1)	
>0–6 standard drinks	181 (31.4)	85 (32.1)		29 (29.0)		479 (31.8)	74 (24.8)	
7–20 standard drinks	180 (31.3)	69 (26.0)		32 (32.0)		482 (32.0)	109 (36.6)	
≥21 standard drinks	110 (19.1)	56 (21.1)		24 (24.0)		291 (19.3)	88 (29.5)	
Frequency of NSAIDs use, n (%)			0.05		0.35			0.16
Never	270 (46.8)	129 (48.5)		49 (48.5)		657 (43.7)	137 (46.3)	
Occasionally	177 (30.7)	70 (6.3)		28 (27.7)		472 (31.4)	77 (26.0)	

Table 1. Comparison of characteristics among cases and controls in study of digestive health and Australian cancer study participants (Continued)

Characteristics	Study of digestive health (SDH)					Australian cancer study (ACS)		
	SDH controls (n=577)	Nondysplastic BE (n=266)	p value[1,2]	Dysplastic BE (n=101)	p value[1,3]	ACS controls (n=1,507)	EAC (n=299)	p value[1,4]
<weekly	62 (10.8)	20 (7.5)		7 (6.9)		145 (9.7)	26 (8.8)	
≥weekly	68 (11.8)	47 (17.7)		17 (16.8)		228 (15.2)	56 (18.9)	
Vitamin C mg day^{-1}; mean±SD	165±73	172±74	0.20	154±63	0.13	169±71	157±65	0.004
Vitamin E mg day^{-1}; mean±SD	7.0±2.1	7.2±2.2	0.43	6.7±2.3	0.16	7.4±2.1	6.8±1.8	<0.0001
β-carotene µg day^{-1}; mean±SD	5205±2724	5290±3361	0.70	4352±2389	0.003	5240±2700	4785±2546	0.007
Selenium µg day^{-1}; mean±SD	46.9±14	46.7±14.9	0.82	45.4±12.0	0.30	46.2±14.3	44.0 (10.2)	0.01
Total energy (kJ); mean±SD	9237±2676	9355±3004	0.57	9347±3051	0.71	9267±2694	10020±3051	<0.0001

Abbreviations: BE, Barretts Esophagus; EAC, Esophageal adenocarcinoma; NSAIDs, non-steroidal anti-inflammatory drugs.
[1]chi-square test for overall p (gender, education, reflux, NSAID use); or chi-square test for trend (BMI, smoking, alcohol); or ANOVA. [2]p value for non-dysplastic BE versus SDH controls. [3]p value for dysplastic BE versus SDH controls. [4]p value for EAC versus ACS controls. [5]1 standard drink = 10g of alcohol

as a categorical variable (control, nondysplastic, and dysplastic BE), using the test statement in SAS. We found that intakes in the fourth quartile of β-carotene (Q4 nondysplastic *vs.* dysplastic BE, Wald chi-square=3.08, P=0.08) and vitamin E (Q4 nondysplastic *vs.* dysplastic BE, Wald chi-square=3.20, P=0.07) from food sources; β-carotene (Q4 nondysplastic *vs.* dysplastic BE, Wald chi-square=3.27, P value=0.07) from food and supplement sources combined; and fruit intake (Q4 nondysplastic *vs.* dysplastic BE, Wald chi-square=3.48, P value=0.06) were different for the two BE case groups with P values approaching significance.

There was no statistically significant effect modification by body mass index, reflux symptoms and smoking on the association between the antioxidants, antioxidant index, fruit and vegetables and risk of EAC, non-dysplastic or dysplastic BE.

Discussion

In these two large population-based case-control studies, we evaluated the association between intake of antioxidants from food sources, antioxidants from food and supplement sources combined, antioxidant index scores, fruit and vegetable intake (major sources of dietary antioxidants) and risk of nondysplastic BE, dysplastic BE and EAC. Our data showed that high intake of antioxidants, a high score on antioxidant index, or a high fruit and vegetable intake was not associated with decreased risk of nondysplastic BE. However, the data was suggestive of a possible influence of antioxidants on risk of dysplastic BE. Formal significance testing between the two BE case groups suggested that high intake of β-carotene and vitamin E from food sources, and high intake of β-carotene from food and supplements combined might be associated with modest decreased risk of dysplastic BE, while high intake of fruits, and possibly vitamin C might be positively associated with nondysplastic BE risk. We also showed that high intake of vitamin E (from food sources, and from food and supplements combined), and a high score on the antioxidant index from food sources were associated with decreased risk of EAC.

Results of our initial analysis with all BE cases showed no association between dietary β-carotene, vitamin C, vitamin E, selenium, and risk of BE. This is consistent with the findings of an Irish study that reported similar results.[22] We have however, extended this study by evaluating the association between these antioxidants and risk of nondysplastic BE, dysplastic BE as well as EAC. It has been proposed that the sequence of events leading from nondysplastic BE to EAC might be driven in part by oxidative stress[13–16,18]; therefore increasing intake of antioxidant nutrients would be expected to be related to lower risks of both precancerous and cancerous lesions. Our data certainly offer no support for an inverse association with nondysplastic BE. Indeed, vitamin C from food sources and fruit intake was associated with increased risk of nondysplastic BE. The highest individual food sources of vitamin C in our study were oranges, orange juice, rock melon, broccoli, tomatoes, sprouts, strawberries, other fruit juices and boiled potato. Together these sources

Table 2. Association between antioxidants from food sources only and risk of non-dysplastic BE, dysplastic BE and EAC[1]

	Study of digestive health					Australian cancer study		
		Nondysplastic BE (n=258)		Dysplastic BE (n=99)		ACS controls (n=1,489)	EAC (n=288)	
Nutrients (median; min–max)	SDH controls (n=569)	n	OR (95% CI)[2]	n	OR (95% CI)[2]	n	N	OR (95% CI)[2]
Antioxidants from food sources								
β-carotene (μg day^{-1})[3]								
Q1 (2301; 270–3478)	141	79	1.00	38	1.00	369	91	1.00
Q2 (4160; 3481–4818)	141	51	0.88 (0.53–1.44)	20	0.67 (0.33–1.36)	373	64	0.79 (0.53–1.17)
Q3 (5577; 4832–6650)	144	60	0.93 (0.57–1.52)	27	1.10 (0.56–2.17)	372	76	0.96 (0.66–1.41)
Q4 (8154; 6664–25647)	143	68	1.06 (0.64–1.74)	14	0.51 (0.23–1.11)	375	57	0.81 (0.53–1.22)
p trend			0.79		0.18			0.44
Vitamin C (mg day^{-1})[3]								
Q1 (96; 29–118)	139	54	1.00	30	1.00	368	76	1.0
Q2 (139; 118–161)	143	64	1.13 (0.68–1.88)	28	0.99 (0.50–1.98)	373	95	1.32 (0.91–1.92)
Q3 (181; 161–205)	143	66	1.09 (0.68–1.91)	16	0.56 (0.26–1.24)	371	63	0.94 (0.63–1.42)
Q4 (245; 205–638)	144	74	1.90 (0.99–2.86)	25	1.16 (0.53–2.53)	377	54	0.79 (0.51–1.20)
p trend			0.05		0.93			0.11
Vitamin E (mg day^{-1})[3]								
Q1 (4.9; 2.0–5.7)	140	57	1.00	32	1.00	370	95	1.0
Q2 (6.3; 5.7–7.0)	143	64	1.24 (0.75–2.07)	29	0.82 (0.42–1.69)	373	74	0.84 (0.58–1.23)
Q3 (7.6; 7.0–8.4)	144	73	1.38 (0.84–2.28)	18	0.73 (0.45–1.52)	373	77	0.96 (0.66–1.40)
Q4 (9.6; 8.4–18.2)	142	64	1.24 (0.73–2.09)	20	0.57 (0.27–1.21)	373	42	0.43 (0.28–0.67)
p trend			0.42		0.13			0.001
Selenium (μg day^{-1})[3]								
Q1 (33; 9–37)	142	71	1.00	22	1.00	368	74	1.0
Q2 (41; 37–44)	144	65	1.03 (0.63–1.67)	30	1.63 (0.83–3.43)	376	83	1.08 (0.74–1.59)
Q3 (48; 44–52)	141	62	1.23 (0.75–2.02)	29	2.24 (1.08–4.48)	371	70	0.93 (0.62–1.38)
Q4 (60; 53–165)	142	60	1.12 (0.68–1.84)	18	1.03 (0.47–2.26)	374	61	1.15 (0.76–1.73)
p trend			0.58		0.95			0.65
Antioxidant index score (from food sources only)[4]								
Q1 (7; 4–8)	172	79	1.00	38	1.00	468	109	1.00
Q2 (10; 9–10)	136	57	1.23 (0.76–2.01)	29	1.71 (0.87–3.38)	366	83	1.00 (0.70, 1.43)
Q3 (11; 11–12)	137	66	1.28 (0.79–2.08)	16	0.56 (0.27–1.19)	342	67	1.04 (0.71, 1.52)
Q4 (14; 13–16)	124	56	1.28 (0.76–2.17)	16	1.02 (0.44–2.33)	313	29	0.49 (0.30–0.80)
p trend			0.32		0.32			0.04

Abbreviations: SDH, study of digestive health; ACS, Australian cancer study; BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; OR, Odds ratio. [1]Observations with missing values on any variable were excluded from analysis. [2]ORs were adjusted for gender, age, education, BMI, esophageal reflux symptoms, lifetime alcoholic drink, total pack-years of smoking, NSAID use, supplement use (ever/never) and total energy (log-transformed). [3]Energy adjusted nutrients using the residual method[34]—Nutrients were categorized to create quartiles such that Q1 (reference group) is the lowest 25% of intake range and Q4 is the highest 25%. [4]Antioxidant index - calculated using antioxidants from food sources only.

contributed almost half the total daily vitamin C intake of controls, nondysplastic and dysplastic BE cases (48, 47 and 46%, respectively). It has been suggested that citrus fruits may lead to reflux but the proportion of vitamin C from citrus fruit did not vary between controls and the two case groups (15, 16 and 15%, respectively) or by the presence or absence of reflux (14 and 15%, respectively). We are unable to explain the observed positive association with nondysplastic BE and regard it as a chance finding. Whilst a few other studies have examined the association between dietary antioxidants and risk of BE,[19–22] none have differentiated between nondysplastic and dysplastic BE. Two reports from one Irish study found a nonsignificant inverse association between vitamin C, vitamin E and risk of BE[22] and a

Table 3. Association between antioxidants from food and supplement combined, food sources only, and risk of BE and EAC[1]

	Study of digestive health					Australian cancer study		
		Nondysplastic BE (n=258)		Dysplastic BE (n=99)		ACS controls (n=1,489)	EAC (n=288)	
Nutrients (median; min–max)	SDH controls (n=569)	n	OR (95% CI)[2]	n	OR (95% CI)[2]	n	N	OR (95% CI)[2]
Total Antioxidants (from food and supplement combined)								
Total β-Carotene (μg day^{-1})[3]								
Q1 2333 (270–3510)	141	77	1.00	39	1.00	370	91	1.00
Q2 4187 (3512–4857)	141	52	0.89 (0.54–1.45)	20	0.67 (0.34–1.34)	372	65	0.82 (0.56–1.21)
Q3 5631 (4857–6725)	144	67	1.07 (0.66–1.74)	27	1.10 (0.56–2.16)	373	72	0.94 (0.64–1.37)
Q4 8317 (6726–25646)	143	62	0.95 (0.58–1.56)	13	0.45 (0.20–1.00)	375	60	0.86 (0.58–1.29)
p trend			0.99		0.16			0.59
Total vitamin C (mg day^{-1})[3]								
Q1 101 (29–131)	140	68	1.00	35	1.00	368	80	1.00
Q2 159 (131–185)	142	66	0.91 (0.56–1.49)	18	0.61 (0.30–1.25)	376	92	1.24 (0.85–1.81)
Q3 216 (185–273)	144	60	0.93 (0.56–1.56)	29	1.12 (0.56–2.24)	371	61	0.86 (0.57–1.29)
Q4 447 (273–3167)	143	64	1.01 (0.60–1.69)	17	0.72 (0.34–1.53)	375	55	0.98 (0.64–1.49)
p trend			0.96		0.73			0.52
Total vitamin E (mg day^{-1})[3]								
Q1 5.3 (2.1–6.2)	140	68	1.00	37	1.00	371	92	1.00
Q2 6.9 (6.2–7.7)	143	59	0.95 (0.58–1.56)	21	0.63 (0.32–1.27)	372	80	0.96 (0.66, 1.40)
Q3 8.5 (7.7–9.9)	143	65	1.04 (0.63–1.70)	17	0.59 (0.28–1.21)	373	61	0.71 (0.48–1.06)
Q4 22.3 (9.9–780)	143	66	0.76 (0.46–1.25)	24	0.58 (0.30–1.16)	374	55	0.64 (0.43–0.96)
p trend			0.36		0.12			0.04
Total selenium (μg day^{-1})[3]								
Q1 33 (9–37)	142	71	1.00	27	1.00	369	73	1.00
Q2 41 (37–44)	144	69	1.19 (0.74–1.94)	25	1.14 (0.57–2.29)	375	87	1.19 (0.81–1.74)
Q3 48 (44–53)	141	57	1.23 (0.74–2.02)	26	1.54 (0.76–3.14)	373	72	1.00 (0.68–1.49)
Q4 63 (53–165)	142	61	1.15 (0.70–1.88)	21	0.98 (0.47–2.03)	373	56	1.08 (0.71–1.65)
p trend			0.59		0.81			0.93
Total Antioxidant index score (from food and supplements combined)[4]								
Q1 7 (4–8)	173	91	1.00	46	1.00	468	109	1.00
Q2 10 (9–10)	146	57	0.92 (0.57–1.47)	21	0.53 (0.27–1.04)	366	83	1.02 (0.72–1.47)
Q3 12 (11–12)	137	54	0.81 (0.50–1.32)	17	0.54 (0.26–1.12)	342	67	0.67 (0.41–1.02)
Q4 14 (13–16)	113	56	1.11 (0.66–1.87)	15	0.72 (0.33–1.55)	313	29	0.75 (0.40–1.15)
p trend			0.94		0.22			0.12

Abbreviations: SDH, study of digestive health; ACS, Australian cancer study; BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; OR, odds ratio.
[1]Observations with missing values on any variable were excluded from analysis. [2]ORs were adjusted for gender, age, education, BMI, esophageal reflux symptoms, lifetime alcoholic drink, total pack-years of smoking, and NSAID use. [3]Energy adjusted nutrients from food sources and supplements combined—nutrients were categorized to create quartiles such that Q1 (reference group) is the lowest 25% of intake range and Q4 is the highest 25%.
[4]Total antioxidant index—calculated using antioxidants from foods and supplements combined.

significant inverse association between fruit but not vegetables and risk of BE.[36] Two North American studies found a significant inverse association between vitamin C[20,21] and risk of BE, while one study found a significant inverse association between vitamin E, β-carotene and risk of BE.[21] Another North American study found a significant association between vegetable intake, and risk of BE.[37] Results of our dysplastic BE, but certainly not nondysplastic BE, are suggestive of a possible influence of antioxidants; thus, our data would suggest that any protective effects of antioxidant nutrients most likely occur after the initial metaplastic change to Barrett's esophagus has already occurred.

Our data adds to previous results that have shown inverse associations between high vitamin E intake, a high

Table 4. Association between fruit and vegetable intake and risk of BE and EAC[1]

	Study of digestive health		
	Nondysplastic BE OR[2] (95% CI)	Dysplastic BE OR[2] (95% CI)	Australian cancer study EAC OR[2] (95% CI)
Number cases/controls	258/568	99/568	288/1488
Fruits (g day^{-1})			
Q1	1.00	1.00	1.00
Q2	2.11 (1.26–3.53)	0.65 (0.30–1.39)	1.19 (0.80–1.77)
Q3	1.39 (0.81–2.40)	1.28 (0.62–2.63)	0.97 (0.64–1.46)
Q4	1.83 (1.02–3.29)	1.19 (0.52–2.70)	0.95 (0.60–1.50)
p trend	0.16	0.42	0.63
Vegetables (g day^{-1})[3]			
Q1	1.00	1.00	1.00
Q2	1.25 (0.76–2.06)	0.68 (0.33–1.41)	0.97 (0.65–1.43)
Q3	1.41 (0.84–2.37)	0.80 (0.39–1.63)	0.67 (0.44–1.02)
Q4	1.13 (0.65–1.96)	0.65 (0.29–1.46)	0.73 (0.47–1.13)
p trend	0.58	0.36	0.06
Total fruit and vegetables (g day^{-1})			
Q1	1.00	1.00	1.00
Q2	1.42 (0.86–2.35)	0.78 (0.37–1.62)	0.98 (0.66–1.46)
Q3	1.11 (0.64–1.92)	1.11 (0.53–2.34)	0.96 (0.63–1.47)
Q4	1.46 (0.82–2.62)	1.08 (0.45–2.59)	0.76 (0.47–1.22)
p trend	0.35	0.67	0.29

Abbreviations: SDH, study of digestive health; ACS, Australia cancer study; BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; OR, odds ratio.
[1]Observations with missing values on any variable were excluded from analysis. [2]OR adjusted for gender, age, education, BMI reflux alcohol intake smoking NSAID use, supplement use, energy (log transformed). [3]Vegetables exclude potato.

antioxidant index score and risk of EAC. Our finding of an inverse association between vitamin E and EAC risk is consistent with some,[38–40] but not all studies,[22,41,42] while the inverse association we found between high antioxidant scores and EAC risk is consistent with studies that have investigated this association.[22,41] The inverse association we observed between vegetable intake and EAC is broadly consistent with the results from two prospective studies[43,44] and one Swedish case-control study.[45]

The strength of our studies includes their relatively large sample sizes, population-based design, and our ability to control for a large number of potentially important confounders. Also, by conducting two case-control studies in parallel, we were able to examine both precancerous lesions and cancer. Limitations include the low participation rate among our ACS potential controls, recall bias with respect to differential reporting of dietary intake, and the possibility that cases might have changed their diet with the onset of disease. The participation rate was low among our ACS controls (51%); however, compared to our SDH controls with a higher participation rate (72%), the distribution of key characteristics was similar, with the exception of smoking where ACS controls were more likely to be smokers (Table 1). Detailed information on the characteristics of nonparticipants is not available because of Australian privacy laws; nevertheless, comparison of ACS control data to Australian National Health Survey data from a representative survey of the Australian adult population conducted in 2004 with a reported 90% response rate,[46] showed similar distributions of key characteristics including ever/never smoking.[47] The strong influence of current diet on recall of past diet might raise concerns regarding the possibility of recall bias among cases if their diet had changed as a result of their diagnosis, or because they experienced symptoms as a result of the presence of subclinical disease before diagnosis. To minimize this, study participants were asked to report recent changes to their diet in the last year or two. We reanalyzed our data excluding those who reported changing their usual eating habits in the previous year and observed no material difference in the estimates obtained.[48]

A potential limitation was that we required the presence of intestinal metaplasia (IM) as a diagnostic criterion for BE, since this was the accepted international definition at the time of study recruitment. Since that time, less stringent definitions have been promulgated which no longer require the presence of IM in biopsy tissues.[49] These new definitions would only introduce appreciable bias for our study if there were many people who would have been considered "cases"

under the less stringent criteria, but who were declared to be "noncases" in our study. We consider the likelihood of such bias to be low. Moreover, such a bias would serve only to attenuate any associations, and thus would render our risk estimates "conservative."

In summary, our findings suggest that high intake of antioxidants may be inversely associated with risk of EAC, and perhaps also play a role in reducing risks of dysplastic BE but not nondysplastic BE. Therefore, whilst oxidative and nitrosative stress have been implicated in the pathogenesis of BE and EAC,[8,13,16,17,49] our data support this hypothesis for EAC and partly for dysplastic BE. It is possible that other antioxidants, such as polyphenolic compounds, may play a role in the development of dysplastic BE and EAC. Our results lend support to the message that high fruit and vegetable intake are important in reducing some cancers. Thus, public health message towards increasing their intake would still be of benefit to patients with BE. Further large observational studies with clear histological distinction between precancers and cancers are required to confirm these observations.

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