HHS Public Access

Author manuscript

Ann Epidemiol. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

Ann Epidemiol. 2015 October ; 25(10): 730–735.e2. doi:10.1016/j.annepidem.2015.05.010.

Dietary flavonoid intake and Barrett's esophagus in western Washington State

Jessica L. Petrick[a,*], **Susan E. Steck**[b], **Patrick T. Bradshaw**[c], **Wong-Ho Chow**[d], **Lawrence S. Engel**[a], **Ka He**[e], **Harvey A. Risch**[f], **Thomas L. Vaughan**[g], and **Marilie D. Gammon**[a]

[a]Department of Epidemiology, University of North Carolina, Chapel Hill, North Carolina

[b]Department of Epidemiology and Biostatistics, University of South Carolina, Columbia, South Carolina

[c]Department of Nutrition, University of North Carolina, Chapel Hill, North Carolina

[d]Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, Texas

[e]Department of Epidemiology and Biostatistics, Indiana University, Bloomington, Indiana

[f]Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, Connecticut

[g]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington

Abstract

Purpose—Flavonoids, concentrated in fruits and vegetables, demonstrate in experimental studies chemopreventive properties in relation to Barrett's esophagus (BE), a precursor lesion for esophageal adenocarcinoma. One case-control investigation reported an inverse association between isoflavone intake and odds of BE, yet no epidemiologic study has considered other flavonoid classes, which are more commonly consumed by Americans.

Methods—We examined intake of total flavonoids, six flavonoid classes, and lignans among case-control study participants in western Washington state. Food frequency questionnaires were self-completed by BE cases with specialized intestinal metaplasia (SIM) (n=170) and matched controls (n=183).

Results—In logistic regression models adjusted for age, sex, body mass index, and energy intake, the odds ratio for SIM BE associated with anthocyanidin intake was 0.49 (95% Confidence Interval: 0.30, 0.80, for quartiles 2-4 combined vs. quartile 1), for which wine and fruit juice were major dietary sources. More moderate decreased odds ratios were noted for flavanones, flavonols,

[*]Correspondence to: Jessica L. Petrick, Department of Epidemiology, CB# 7435, University of North Carolina, Chapel Hill, NC 27599-7435 (jessica.petrick@unc.edu).

isoflavones, and lignans. A modest increased odds ratio was observed for flavones, for which pizza was the main dietary source in our population.

Conclusions—Our findings of an inverse association between anthocyanidins and odds of BE suggests that adequate dietary intake of these compounds may lower risk of this cancer precursor lesion.

Keywords

Barrett's esophagus; diet; epidemiologic studies; flavonoids

Introduction

Over the last two decades, the incidence rate for esophageal adenocarcinoma has been among the most rapidly increasing of any cancer type in the United States (U.S.) [1, 2]. Esophageal adenocarcinoma is thought to arise in Barrett's esophagus (BE), specialized intestinal metaplasia of the lower esophageal epithelium [3]. Studying precursor lesions may provide insight into the etiology of cancer by elucidating risk factors that act early in disease initiation. Epidemiologic studies have shown that diets high in fruit and vegetable intake are inversely associated with odds of BE [4]. Flavonoids, a group of bioactive polyphenolic compounds naturally occurring in fruits, vegetables, and beverages of plant origin, may partially account for the inverse dietary association of fruits and vegetables with BE [5, 6].

Experimental studies support the hypothesis of an inverse association between flavonoid exposure and BE. For example, flavan-3-ol inhibited BE cell growth through down-regulation of cyclin D1 protein expression [7]. Lignans are other polyphenolic compounds that have antioxidant properties, anti-inflammatory and pro-apoptosis effects, and promote cell cycle arrest [8]. One epidemiologic investigation to date has examined the association between dietary flavonoid intake and odds of BE. This Texas case-control study of 151 BE cases, considered one class of flavonoids, isoflavones, and found an inverse association [9]. However, intake of isoflavone-containing foods in the U.S. is limited; whereas the other five flavonoid classes are found in foods more commonly consumed by Americans [10], yet their associations with BE have not been considered.

To determine whether intakes of total flavonoids or specific flavonoid classes are associated with odds of BE, we compared flavonoid intake between patients newly diagnosed with BE and general population controls who participated in a community-based case-control study.

Materials and Methods

To conduct this ancillary study, we built upon resources collected for the Study of Reflux Disease, a case-control investigation conducted in western Washington state [11, 12]. This study was approved by the Institutional Review Boards of the participating institutions.

Study Population

Eligible case participants were men and women, aged 20-80 years without previously diagnosed BE who underwent upper endoscopy for gastroesophageal reflux disease (GERD)

symptoms between 1997 and 2000 at community gastroenterology clinics. Consenting participants had four-quadrant biopsy specimens collected. Specimens were evaluated by one of three university-based pathologists, who were blinded to the endoscopy findings. BE was considered present if at least one biopsy specimen had specialized intestinal metaplasia (SIM). Case participants were classified into one, two, or three diagnostic categories indicating disease progression, based on the presence (and length) or absence of visible columnar epithelium [visible BE (VBE)] during endoscopy: 1) SIM (i.e., all cases), 2) SIM and VBE (VBE cases), and 3) SIM and VBE greater than two centimeters [long-segment BE (LSBE) cases]. The first and most inclusive category (SIM cases) adheres to the concept of "ultra-short segment BE" [13]. The latter two categories were selected because they are consistent with the American College of Gastroenterology definition of BE [14], enhancing the clinical relevance of our study results.

Community-based control participants were identified using a modified Waksberg random digit dialing technique [15], which identifies individuals living in the same geographic area as case participants [16]. Controls were matched to cases on age (±3 years) and sex.

In the parent study, SIM was identified in 208 individuals providing biopsy specimens. However, only 193 of these cases successfully completed interviews. Thus, study participants included 193 cases (92.8% of eligible) and 211 community controls (68.7% of eligible) [11]. Of those, 87.4% (170 cases, 183 controls) provided adequate dietary intake information (see Exposure Assessment below) and are the focus of the current report. Their demographic characteristics are shown in Supplementary Table 1.

Exposure Assessment

Information on potential risk factors was obtained by a 45-minute structured questionnaire administered face-to-face by trained interviewers. The time between endoscopy and interview for case participants was 1-2 months. Written informed consent was obtained from each participant prior to interview.

Dietary intake for the one year prior to interview was assessed by a validated self-administered, 131-item food frequency questionnaire (FFQ) [17]. In total, 177 cases (91.7%) and 192 controls (91.0%) completed FFQs. Individuals with estimated total energy intake of <500 or >4,000 kilocalories/day for women or <800 or >5,000 kilocalories/day for men were excluded based on implausible energy intake (7 cases, 9 controls) [12, 18].

Assessment of Dietary Flavonoid Intake

Intakes of total flavonoids, six classes of flavonoids (anthocyanidins, flavan-3-ols, flavanones, flavones, flavonols, and isoflavones), and lignans was estimated from 91 food and beverage FFQ items that contained measureable amounts of flavonoids [19-21]. A study-specific flavonoid database was developed by linking the FFQ data with the 2011 U.S. Department of Agriculture (USDA) Database for the Flavonoid Content of Selected Foods [19] and the 2008 USDA-Iowa State University Database on the Isoflavone Content of Selected Foods [20]. To assess lignan content, specifically secoisolariciresinol and matairesinol, we utilized data from foods consumed by a North American population [21].

Some FFQ items represented groups of foods or beverages. For flavonoid intake calculations, the individual foods and beverages represented in a single item were weighted, based on the relative frequency of consumption in the general American population [17]. For example, the FFQ item of "apples and pears" was assigned a weight of 0.75 for "apples" and 0.25 for "pears." To calculate the flavonoid intake, the weight assigned to each food in the FFQ item was multiplied by the flavonoid content of that food, summed across all foods in the FFQ item, and then multiplied by the number of times consumed per day and by the serving size [10].

Statistical Analysis

Unconditional logistic regression was used to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the association between flavonoid intakes and odds of BE. Conditional logistic regression was also performed on matched pairs of cases and controls [22]. Results were similar; therefore, only unconditional logistic regression results are reported. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Flavonoid intakes were categorized in quartiles, based on the distributions of intakes among the control participants [18]. To examine linear trend, we also utilized restricted quadratic spline coding (Supplementary Figure 1). Tests for linear trends were based on continuous flavonoid values in mg/day.

Effect measure modification by cigarette smoking (evaluated as continuous pack-years and as dichotomous, ever/never) and body mass index (BMI, kg/m^2) at interview (evaluated as continuous and as dichotomous, <25 or ≥25 kg/m^2) was assessed using likelihood ratio tests to compare regression models with and without a multiplicative term [22]; there was no evidence of effect measure modification by either covariate ($p \geq 0.05$) on the association between total flavonoid intake and BE in any of the models.

Potential confounders included BMI (evaluated as continuous and as dichotomous, <25 or ≥25 kg/m^2), race (white, other), income (<$45,000, ≥$45,000-74,999, ≥$75,000), education (≤high school, technical school, ≥college), and cigarette smoking (evaluated as ever/never and continuous pack-years). If variable elimination changed the log odds ratio by ≥10%, the variable was considered a confounder and included in the model [22]; only BMI met this criterion. Total energy intake was included for adjustment on an *a priori* basis [23]. Thus, the final models included BMI (continuous), total energy intake (kilocalories, continuous), and the matching factors age (continuous) and sex.

To determine whether associations with flavonoids varied by diagnostic category, BE patients were categorized into progressively more exclusive groups by segment length [13] and then each case subgroup was compared to all controls. To explore the threshold associations seen in restricted quadratic splines (Supplementary Figure 1), we dichotomized exposures and compared the bottom quartile versus the upper three quartiles.

Sensitivity Analysis

The USDA Flavonoid Database assigns a value of 7.39 mg/100 g of banana for anthocyanidins [19], which is controversial [24]. We therefore conducted a sensitivity

analysis excluding the anthocyanidin value for bananas, which did not substantially alter our results (Supplementary Tables 2-5).

Results

As shown in Table 1 for this western Washington study population, control participants consumed similar amounts of total flavonoids (median=75.37 mg/day) as BE case participants (median=75.55 mg/day). However, control participants consumed a smaller dietary intake of flavan-3-ols (median=17.35 mg/day), which were the largest contributor to total flavonoid intake, than case participants (median=25.56 mg/day).

Table 2 lists the major sources of flavonoids among the control participants. For total flavonoids, 47.2% of mean intake was from black tea (58.96 mg/day), 12.2% from orange/grapefruit juice (15.31 mg/day), and 6.8% from wine (8.48 mg/day). Black tea contains flavan-3-ols, flavonols, and lignans; orange/grapefruit juice contains flavanones, flavonols, isoflavones, and lignans; and wine contains anthocyanidins, flavan-3-ols, flavanones, flavones, flavonols, and lignans.

Odds of BE was modestly reduced in relation to intake of anthocyanidins (highest versus lowest quartile of intake, OR=0.59, 95% CI=0.31-1.12), flavanones (OR=0.71, 95% CI=0.37-1.35), flavonols (OR=0.89, 95% CI=0.47-1.69), isoflavones (OR=0.68, 95% CI=0.34-1.36), and lignans (OR=0.64, 95% CI=0.32-1.26), but the confidence intervals were wide and included the null (Table 3). In contrast, there was little or no association between total flavonoids (OR=1.09, 95% CI=0.56-2.11) or flavan-3-ols (OR=0.88, 95% CI=0.45-1.71) and odds of BE. A modest increased odds of BE was observed for flavones (OR=1.26, 95% CI=0.63-2.52).

As presented in Table 4, the strength of inverse associations between flavonoid intake and BE appeared to increase with increasing disease specificity. For example, comparing the upper three quartiles to the bottom one, the odds ratio for the association with anthocyanidin intake (for which wine, bananas and fruit juice were the major dietary sources) was reduced by 51% for SIM (which includes all cases, OR=0.49, 95% CI=0.30-0.80), by 44% for VBE (OR=0.56, 95% CI=0.31-1.02), and by 56% for LSBE (OR=0.44, 95% CI=0.21-0.92). The corresponding odds reductions were similarly pronounced for LSBE and flavanones (OR=0.49, 95% CI=0.24-1.00) and flavonols (OR=0.53, 95% CI=0.24-1.17), but included the null value.

Discussion

This is the first epidemiologic study to examine the association between total and all classes of flavonoid and lignan intakes and odds of BE. In our analysis, we found modest, imprecise decreases in the odds ratios with increasing intakes of anthocyanidins, flavanones, flavonols, isoflavones, and lignans when all BE stages were considered together. While we did not observe a significant trend, the inverse associations for anthocyanidins, flavanones, and flavonols were slightly more pronounced when we considered segment length. For example, odds reductions ranged from 47 to 56% for LSBE in relation to these flavonoid classes.

Our findings are consistent with the one previous epidemiologic study that found a decreased odds of BE associated with dietary isoflavone intake [9]. Foods containing high levels of isoflavones are infrequently consumed in the U.S. [10], which is consistent with reports from our study population (Table 1). In our study we observed a suggested odds reduction for BE in relation to anthocyanidin intake. Our findings are consistent with interim clinical trial results that found reduced markers of oxidative stress in BE patients consuming anthocyanidin-rich freeze-dried black raspberries [25].

BE is a potential precursor lesion of esophageal adenocarcinoma, thus risk factors for this lesion could be involved in tumor initiation or promotion, whereas factors associated with tumor invasion should be more closely involved in cancer progression [26]. Our finding of a possible inverse association between anthocyanidin intake and BE is consistent with two previous studies of esophageal adenocarcinoma conducted in the U.S. [27, 28] that found a significant decrease in odds of invasive cancer associated with increased anthocyanidin intake. These observations suggest that anthocyanidin may play a role in both initiation and progression of esophageal adenocarcinoma. Flavanones [28], flavonols [28], isoflavones [27], and lignans [28] have also been associated with a decreased odds of invasive esophageal adenocarcinoma, but the literature is not consistent.

In this study, we observed possible odds reductions for the associations between anthocyanidins, flavanones, and flavonols in relation to all diagnostic BE categories. Importantly, BE segment length is related to esophageal adenocarcinoma risk [29]. However, our study population included a limited number of patients with VBE or LSBE. Because of data sparseness when we examined associations with the case participants categorized by segment length and potential threshold effects seen in the main analysis (Table 3), we grouped flavonoid intake into two categories, rather than four [22]. Categorization of flavonoid exposures into two categories for the segment length analysis was conducted after examining the spline analysis by collapsing quartiles 2-4 versus quartile 1. Therefore, results from these subgroup analyses should be interpreted with caution. While these data were collapsed due to potential threshold effects, another possibility is that significant trends could be masked due to misclassification error. Thus, more studies are needed to determine if these associations are due to threshold effects or misclassification errors.

Our findings do not support an inverse association between total flavonoid intake or flavan-3-ol intake and odds of BE. Additionally, a modest increased odds of BE was observed for flavones. These results are at odds with experimental studies that have shown flavan-3-ols and flavones to have important chemopreventive effects against BE [7, 30]. However, it is important to note that these experimental studies administered pure flavonoids derived from plants – green tea and *Dysoxylum binectariferum*; whereas, our study utilized dietary intake of flavonoids from various foods and beverages. We found that the main sources of flavan-3-ols and flavones in our study population were black tea and pizza, respectively. Thus, our observation of an increased odds of BE associated with flavone intake may be confounded by other dietary habits and lifestyle choices linked to high pizza intake.

A recent report used data from the same parent study as we do here, and found an inverse association between fruit and vegetable intake and BE [12]. Flavonoids are concentrated in fruits and vegetables [31]; therefore, flavonoid intake may be a marker for some other factor associated with a healthy diet and lifestyle, rather than act as a causative factor itself [12]. The parent study assessed a number of relevant lifestyle factors, including cigarette smoking, alcohol intake, and BMI [11]; however, in our ancillary study, BMI was the only covariate that influenced our results and was included in the final adjusted models.

A potential source of error in estimating flavonoid content in food, especially in fruits and vegetables, is the variability of environmental conditions, horticultural practices, degree of ripeness, plant variety, storage conditions, industrial processing, and cooking methods, all of which may vary regionally and over time [19, 20, 31]. Organically and sustainably grown foods, compared to those produced by conventional methods, also have higher polyphenol concentrations [32]. Thus, food items reportedly consumed by this study population may differ from the foods utilized to create the estimates included in the databases [19-21]. To estimate the impact such influences, the USDA Food Composition and Nutrient Data Laboratories determined the flavonoid content for more than 60 fruits, vegetables, and nuts by sampling foods from four U.S. regions during two seasons of the year. While flavonoid content variability was high within and between foods, the average flavonoid content was similar to values reported in the USDA databases [33]. Additionally, the FFQ line item for wine did not distinguish between red and white wine, which have different concentrations of flavonoids. Therefore, the FFQ assigned the weight for the wine line item as 50% white wine and 50% red wine, based on the relative frequency of consumption in the general American population. However, individuals often preferentially drink white or red wine. Thus, individual participant's estimates of flavonoid classes for which wine is a source may have some degree of misclassification.

Another potential source of error in estimating an association between flavonoid intake and odds of BE is the bioavailability of flavonoid compounds. Little is known about the absorption of flavonoids in the body, and metabolism of flavonoids varies by individual [34]. Additionally, currently measured flavonoid biomarkers are of limited usefulness in epidemiologic studies because of the variation in absorption profiles, with maximum concentrations reached between 0.5-9 hours after dietary intake [34]. Thus, these biomarkers may not be highly correlated with usual adult dietary intake, which is the target exposure for cancer etiology studies, including studies of precursor lesions. While variation in dietary flavonoid content and flavonoid bioavailability may be a study limitation, it is a common limitation for all studies that rely on nutritional databases to estimate dietary intakes [18].

Patients with GERD symptoms are recommended to omit foods that are chemically or mechanically irritating [35]; therefore, BE patients may have already made changes to their usual diets by the time of FFQ administration. Foods that are irritating vary by individual [36], so we are unable to determine how such potential changes in diet could have affected our flavonoid intake estimates. While some flavonoid-containing foods may be recommended for GERD patients to avoid (e.g., coffee, tea, alcohol, citrus, tomatoes, chocolate, peppers, and onions), one dietary study showed that intakes of fruits, vegetables, and alcohol did not differ by symptomatic GERD status [37]. As all cases in this study had

GERD, it is still possible that the association between BE and flavonoid intake is due to reverse causation.

For a FFQ, assessing diet for the year prior to diagnosis is a standard time interval, as it does not require extensive recall [18]. Responses are assumed to reflect usual adult diet. Whether the time period assessed accurately reflects intakes during the time relevant to BE development is unknown. However, because all existing studies conducted among BE patients have relied on a FFQ [12, 38, 39], a cohort study would be required, with employment of multiple alternative dietary assessment methods repeatedly over time, to overcome the limitations of existing studies. Such an alternative study design would be inefficient, because only 10-15% of symptomatic GERD patients develop BE in their lifetime [40].

Our study FFQ did not assess dietary supplement use. Clinical studies of flavonoid supplements began in the early 1990s [41], and a U.S. patent was granted for *Ginkgo biloba* extract, EGb 761, in 1995 [42]. Thus, it is unlikely that use was widespread during this study time period.

The difference that we observed in mean intake of total flavonoids between case and control participants was minimal, roughly equivalent to half of a medium apple per week. However, absolute differences in dietary flavonoid intakes need to be interpreted with caution, as a FFQ was utilized to collect relative, not absolute, dietary information. While FFQs have acknowledged measurement errors, they are useful for ranking individuals' dietary intake relative to one another, which was our primary objective [18].

In summary, our finding of modest inverse associations between anthocyanidins, flavanones and flavonols in relation to BE suggests that dietary intake of these compounds may lower the odds of this precursor lesion. Our findings here, particularly with regard to anthocyanidins, are consistent with our results for esophageal adenocarcinoma [28], suggesting that these compounds could potentially be used across the BE-esophageal adenocarcinoma continuum in an effort to reduce mortality due to these fatal cancers. This is the first epidemiologic study to examine the association between the six flavonoid classes, total flavonoids and lignans and BE; therefore, further research is needed before definite conclusions can be made about the role of dietary flavonoids and lignans in relation to odds of BE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This research was supported in part by grants from the National Institutes of Health (R03CA159409-02, T32CA009330-25, T32ES007018, P30ES10126, R01CA72866).

Thank-you to: Eric Meier, Lynn Onstad, and Patricia Christopherson from the Fred Hutchison Cancer Research Center for their help in providing data and food frequency questionnaire expertise.

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Abbreviations

BE	Barrett's esophagus
CI	confidence interval
FFQ	food frequency questionnaire
GERD	gastroesophageal reflux disease
LSBE	long-segment Barrett's esophagus
OR	odds ratio
SIM	specialized intestinal metaplasia
U.S.	United States
USDA	United States Department of Agriculture
VBE	visible Barrett's esophagus

Table 1

Mean Intakes (mg/day) of Flavonoids and Lignans Among Cases and Controls With Information on Dietary Intake, Study of Reflux Disease, Western Washington State, 1997-2000.

	Controls (N=183)			Cases (N=170)			
	Mean	Standard Deviation	Range	Mean	Standard Deviation	Range	p-value*
Total Flavonoids	125.03	123.10	5.83-819.34	123.55	134.39	10.52-707.45	0.91
Anthocyanidins	13.84	10.67	0.29-55.42	13.47	13.15	0.36-85.19	0.79
Flavan-3-ols	73.01	114.23	1.71-739.93	78.06	125.34	1.85-659.00	0.69
Flavanones	21.97	26.08	0.01-143.37	17.20	21.62	0.02-146.23	0.06
Flavones	2.19	1.56	0.19-11.69	2.15	1.19	0.13-6.68	0.79
Flavonols	11.89	6.63	1.74-42.60	11.47	6.87	2.04-39.00	0.57
Isoflavones	2.14	5.90	0.02-55.18	1.20	2.55	0.04-19.95	0.05
Lignans	0.056	0.029	0.011-0.160	0.051	0.030	0.009-0.176	0.11

* T-test comparing the means of cases and controls.

Table 2

Major Dietary Sources of Flavonoids and Lignans Among a Community-based Sample of Control Participants Without Barrett's Esophagus, Study of Reflux Disease, Western Washington State, 1997-2000.

Flavonoid/Phytoestrogen Class	Representative Flavonoids	Main FFQ* Line Item Sources (%)
Total Flavonoids		Black tea (47.2), orange/grapefruit juice (12.2), wine (6.8), oranges/grapefruit (4.7), apples/pears (3.5), bananas (3.0)
Anthocyanidins	Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin	Wine (31.2), bananas (14.8), fruit juice (11.3), fruit cocktail/applesauce (8.5), strawberries/kiwi (8.0), apples/pears (7.6), bean soups (5.5)
Flavan-3-ols	(+)-Catechin, (+)-Catechin-3-gallate, (-)-Epicatechin, (-)-Epicatechin-3-gallate, (-)-Epigallocatechin, (-)-Epigallocatechin-3-gallate, (+)-Gallocatechin, (+)-Gallocatechin-3-gallate, Theaflavin, Theaflavin-3-gallate, Theaflavin-3′-gallate, Theaflavin-3,3′-digallate, Thearubigins	Black tea (78.2), green tea (3.5), wine (3.3), apples/pears (3.0), beer (2.7), bananas (2.3)
Flavanones	Eriodictyol, Hesperetin, Naringenin	Orange/grapefruit juice (68.6), oranges/grapefruit (26.3), wine (2.8)
Flavones	Apigenin, Luteolin	Pizza (38.4), wine (12.4), vegetable soup (8.0), cream soup (6.8), mixed salad (6.1)
Flavonols	Isorhamnetin, Kaempferol, Myricetin, Quercetin	Black tea (15.6), onions (11.0), apples/pears (9.4), wine (7.2), mixed salad (5.9), beer (5.7)
Isoflavones	Daidzein, Genistein, Glycitein	Tofu (76.5), coffee (5.9), chili with beans (5.7), milk (5.2)
Lignans	Matairesinol, Secoisolariciresinol	Coffee (31.0), wine (12.6), orange/grapefruit juice (9.4), onions (3.8), peanuts (3.7), black tea (3.5)

*FFQ: Food frequency questionnaire.

Table 3

Adjusted* Odds Ratios (OR) and 95% Confidence Intervals (CI) for the Association Between Flavonoid and Lignan Intakes and Barrett's Esophagus, Study of Reflux Disease, Western Washington State, 1997-2000.

Variable and intake (mg/day)	Controls (N=183)	Cases (N=170)	OR	95% CI
Total Flavonoids				
0-42.38	46	44	1.00	
42.39-75.36	46	41	1.10	0.59, 2.08
75.37-166.98	45	46	1.37	0.73, 2.58
≥166.99	46	39	1.09	0.56, 2.11
P for trend†			0.81	
Anthocyanidins				
0-6.12	46	64	1.00	
6.13-9.82	45	24	0.33	0.17, 0.63
9.83-18.26	47	46	0.58	0.32, 1.06
≥18.27	45	36	0.59	0.31, 1.12
P for trend†			0.91	
Flavan-3-ols				
0-9.50	45	44	1.00	
9.51-17.35	46	22	0.51	0.25, 1.03
17.36-107.34	46	70	1.78	0.98, 3.23
≥107.35	46	34	0.88	0.45, 1.71
P for trend†			0.54	
Flavanones				
0-3.80	45	55	1.00	
3.81-12.90	47	41	0.71	0.39, 1.32
12.91-29.64	46	41	0.81	0.44, 1.48
≥29.65	45	33	0.71	0.37, 1.35
P for trend†			0.27	
Flavones				
0-1.15	46	37	1.00	
1.16-1.88	46	39	1.10	0.57, 2.13
1.89-2.82	45	49	1.46	0.75, 2.85
≥2.83	46	45	1.26	0.63, 2.52
P for trend†			0.61	
Flavonols				
0-6.99	46	52	1.00	
7.00-10.86	46	44	0.83	0.45, 1.53
10.87-14.89	46	28	0.60	0.31, 1.16
≥14.90	45	46	0.89	0.47, 1.69
P for trend†			0.50	
Isoflavones				

Variable and intake (mg/day)	Controls (N=183)	Cases (N=170)	OR	95% CI
0-0.24	46	41	1.00	
0.25-0.52	45	56	1.22	0.65, 2.29
0.53-1.16	47	39	0.82	0.42, 1.60
≥1.17	45	34	0.68	0.34, 1.36
P for trend[†]			0.09	
Lignans				
0-0.033	45	53	1.00	
0.034-0.051	46	52	0.91	0.50, 1.67
0.052-0.070	46	28	0.46	0.22, 0.94
≥0.071	46	37	0.64	0.32, 1.26
P for trend[†]			0.15	

[*] Adjusted for age (continuous), sex, body mass index (continuous), and kilocalories (continuous).

[†] P-value for trend for continuous variable.

Table 4

Adjusted* Odds Ratios (OR) and 95% Confidence Intervals (CI) for the Association Between Flavonoid and Lignan Intakes and Barrett's Esophagus Segment Length,[2] Study of Reflux Disease, Western Washington State, 1997-2000.

		Clinical SIM†				Clinical VBE†				Clinical LSBE†			
Variable and intake (mg/day)	**Controls (N=183)**	**Cases (N=170)**	**OR**	**95% CI**	**P for trend‡**	**Cases (N=86)**	**OR**	**95% CI**	**P for trend‡**	**Cases (N=48)**	**OR**	**95% CI**	**P for trend‡**
Total Flavonoids													
0-42.38	46	44	1.00			25	1.00			16	1.00		
≥42.39	137	126	1.19	0.70, 2.01	0.81	61	0.93	0.50, 1.73	0.97	32	0.71	0.33, 1.52	0.70
Anthocyanidins													
0-6.12	46	64	1.00			31	1.00			20	1.00		
≥6.13	137	106	0.49	0.30, 0.80	0.91	55	0.56	0.31, 1.02	0.45	28	0.44	0.21, 0.92	0.67
Flavan-3-ols													
0-9.50	45	44	1.00			20	1.00			15	1.00		
≥9.51	138	126	1.06	0.63, 1.78	0.54	66	1.21	0.63, 2.32	0.81	33	0.75	0.35, 1.60	0.95
Flavanones													
0-3.80	45	55	1.00			31	1.00			20	1.00		
≥3.81	138	115	0.74	0.45, 1.22	0.27	55	0.55	0.31, 0.99	0.38	28	0.49	0.24, 1.00	0.12
Flavones													
0-1.15	46	37	1.00			20	1.00			10	1.00		
≥1.16	137	133	1.25	0.71, 2.20	0.61	66	1.11	0.56, 2.19	0.42	38	1.66	0.67, 4.15	0.96
Flavonols													
0-6.99	46	52	1.00			29	1.00			17	1.00		
≥7.00	137	118	0.77	0.46, 1.30	0.50	57	0.59	0.31, 1.10	0.48	31	0.53	0.24, 1.17	0.63
Isoflavones													
0-0.24	46	41	1.00			20	1.00			9	1.00		
≥0.25	137	129	0.92	0.53, 1.60	0.09	66	0.82	0.41, 1.61	0.35	39	0.98	0.40, 2.42	0.30
Lignans													
0-0.033	45	53	1.00			24	1.00			10	1.00		
≥0.034	138	117	0.71	0.41, 1.21	0.15	62	0.80	0.42, 1.54	0.13	38	1.35	0.56, 3.26	0.52

[*] Adjusted for age (continuous), sex, body mass index (continuous), and kilocalories (continuous).

[†] Barrett's esophagus segment length categories are non-mutually exclusive groups. SIM: Specialized intestinal metaplasia (i.e., all cases), VBE: visible Barrett's esophagus (i.e., SIM with VBE), LSBE: long-segment Barrett's esophagus (i.e., SIM with VBE greater than two centimeters).

[‡] P-value for trend for continuous variable.