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Dietary intake of flavonoids and oesophageal and gastric cancer: incidence and survival in the United States of America (USA)

J L Petrick*[,1], S E Steck[2], P T Bradshaw[3], K F Trivers[4], P E Abrahamson[5], L S Engel[1], K He[6], W-H Chow[7], S T Mayne[8], H A Risch[8], T L Vaughan[9] and M D Gammon[1]

[1]Department of Epidemiology, CB 7435, University of North Carolina, Chapel Hill, NC 27599-7435, USA; [2]Department of Epidemiology and Biostatistics, University of South Carolina, Columbia, SC, USA; [3]Department of Nutrition, University of North Carolina, Chapel Hill, NC, USA; [4]Division of Cancer Prevention and Control, Centers for Disease Control, Atlanta, GA, USA; [5]Salmon Bay Consulting, Inc., Seattle, WA, USA; [6]Department of Epidemiology and Biostatistics, Indiana University, Bloomington, IN, USA; [7]Department of Epidemiology, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [8]Department of Chronic Disease Epidemiology, Yale School of Public Health and Yale Cancer Center, New Haven, CT, USA and [9]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Background: Flavonoids, polyphenolic compounds concentrated in fruits and vegetables, have experimentally demonstrated chemopreventive effects against oesophageal and gastric cancer. Few epidemiologic studies have examined flavonoid intake and incidence of these cancers, and none have considered survival.

Methods: In this USA multicentre population-based study, case participants (diagnosed during 1993–1995 with oesophageal adenocarcinoma (OEA, $n=274$), gastric cardia adenocarcinoma (GCA, $n=248$), oesophageal squamous cell carcinoma (OES, $n=191$), and other gastric adenocarcinoma (OGA, $n=341$)) and frequency-matched controls ($n=662$) were interviewed. Food frequency questionnaire responses were linked with USDA Flavonoid Databases and available literature for six flavonoid classes and lignans. Case participants were followed until 2000 for vital status. Multivariable-adjusted odds ratios (ORs) and hazard ratios (HRs) (95% confidence intervals (CIs)) were estimated, comparing highest with lowest intake quartiles, using polytomous logistic and proportional hazards regressions, respectively.

Results: Little or no consistent association was found for total flavonoid intake (main population sources: black tea, orange/grapefruit juice, and wine) and incidence or survival for any tumour type. Intake of anthocyanidins, common in wine and fruit juice, was associated with a 57% reduction in the risk of incident OEA (OR = 0.43, 95% CI = 0.29–0.66) and OES (OR = 0.43, 95% CI = 0.26–0.70). The ORs for isoflavones, for which coffee was the main source, were increased for all tumours, except OES. Anthocyanidins were associated with decreased risk of mortality for GCA (HR = 0.63, 95% CI = 0.42–0.95) and modestly for OEA (HR = 0.87, 95% CI = 0.60–1.26), but CIs were wide.

Conclusions: Our findings, if confirmed, suggest that increased dietary anthocyanidin intake may reduce incidence and improve survival for these cancers.

Over the past two decades, oesophageal adenocarcinoma (OEA) and gastric cardia adenocarcinoma (GCA) have been among the most rapidly increasing cancer types in the United States and other Western countries (Devesa *et al*, 1998; Simard *et al*, 2012). Oesophageal adenocarcinoma and GCA are often considered as one clinical entity because they are both epithelial cancers

*Correspondence: Dr JL Petrick; E-mail: jessica.petrick@unc.edu

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originating in or near the gastroesophageal junction and have similar 5-year survival rates of ~26% (Wijnhoven *et al*, 1999). Still, oesophageal squamous cell carcinoma (OES) and other (non-cardia) gastric adenocarcinoma (OGA) are the most common forms of oesophageal and gastric cancer worldwide. In addition to geographic variation, these four cancer types have differing risk factors (Hongo *et al*, 2009; de Martel *et al*, 2013). Thus, considering them as distinct entities will help to elucidate the underlying aetiology.

Epidemiologic studies have shown that diets high in fruits and vegetables are inversely associated with oesophageal and gastric cancer incidence (Lunet *et al*, 2007; Li *et al*, 2014). Flavonoids, which are a group of bioactive polyphenolic compounds naturally occurring in fruits, vegetables, and beverages of plant origin, have been hypothesised to account at least partially for such risk reductions (Pierini *et al*, 2008). Experimental studies have supported this hypothesis. For example, freeze-dried berries, which are high in anthocyanidins, inhibited 24–56% of oesophageal tumour multiplicity (average number of tumours per oesophagus) and 8–21% of incidence in rats caused by *N*-nitrosomethylbenzylamine compared with controls (Stoner *et al*, 2006). In addition, Flavopiridol, a synthetic flavone, has been studied in small phase I and II clinical trials in patients with metastatic gastric cancer but was an inactive chemopreventive strategy (Schwartz *et al*, 2001). However, this clinical trial was undertaken without any epidemiologic evidence to support the use of flavonoids. Lignans are another group of polyphenolic compounds that have anti-inflammatory and pro-apoptotic effects, antioxidant properties, and promote cell cycle arrest (Huang *et al*, 2010).

Recent epidemiological investigations conducted in the United States (Bobe *et al*, 2009), Greece (Lagiou *et al*, 2004), Italy (Rossi *et al*, 2007, 2010), Europe (Zamora-Ros *et al*, 2012; Vermeulen *et al*, 2013), Sweden (Ekstrom *et al*, 2011), China (Sun *et al*, 2002), and Mexico (Hernandez-Ramirez *et al*, 2009) have analysed associations between flavonoid or lignan intake and oesophageal or gastric cancer incidence. However, no epidemiologic studies to date have examined associations between flavonoid intake and survival among oesophageal or gastric cancer patients. Clarification of whether total flavonoids, or specific flavonoid classes, influence the incidence of these tumour subtypes or survival once diagnosed would provide empirical support for developing potential risk reduction strategies utilising these compounds.

In this population-based study, we investigated whether intakes of total flavonoids, including specific flavonoid classes, and lignans are associated with: (1) oesophageal or gastric cancer incidence and (2) survival among individuals diagnosed with oesophageal or gastric cancer. For both aims, we consider associations for all four cancer types separately.

MATERIALS AND METHODS

To conduct this ancillary study, we built upon the resources from the USA Multicenter Study, a population-based investigation conducted in the state of Connecticut (CT, principal investigator (PI): HA Risch), a 15-county area of New Jersey (NJ, PI: MD Gammon), and a three-county area of western Washington state (WA, PI: TL Vaughan), which was initiated as a case-control study (Gammon *et al*, 1997) and then continued as a follow-up study to determine vital status among the cases (Trivers *et al*, 2005). This study was approved by all Institutional Review Boards of the participating institutions.

Study population. The three geographic areas (CT, NJ, and WA) each had a population-based cancer registry that was used to identify the cases through rapid reporting methods. Eligible case participants were English-speaking men and women between the ages of 30 and 79 years, diagnosed with a first primary invasive oesophageal or stomach cancer between 1993 and 1995. The parent study goal was to recruit all individuals newly diagnosed with OEA and GCA (which were considered the target case participants), whereas participants with OES or OGA (i.e., comparison cases) were frequency matched to the expected target case participants by geographic location and 5-year age group (CT, NJ, and WA), sex (NJ and WA), and race (white or other, NJ). Final determination of case participant eligibility and classification was made by study pathologists (Drs Heidi Rotterdam at Columbia University for NJ and A Brian West at New York University for CT and WA) after review of medical records and pathology specimens (Gammon *et al*, 1997).

Population-based control participants were frequency matched to the target case participants by 5-year age group and sex. Control participants 30–64 years of age were identified using a modified Waksberg random digit dialing technique (Waksberg, 1978). Control participants 65–79 years of age were identified by random sampling of Health Care Financing Administration rosters (now Centers for Medicare and Medicaid Services) (Gammon *et al*, 1997).

Study participants included 293 individuals with OEA and 261 with GCA (80.6% of eligible target case participants), 221 with OES and 368 with OGA (74.1% of eligible comparison case participants), and 695 population control participants (74.1% of eligible control participants) (Gammon *et al*, 1997). The 93.4% of participants with dietary intake information are the focus of the current study, and the distribution of the demographic characteristics of this subsample did not differ substantially from those of all study participants (Mayne *et al*, 2001) (Supplementary Table 1). Males comprised 83.9% of target cases, 72.9% of comparison cases, and 79.8% of controls; 98.1% of target cases, 83.3% of comparison cases, and 93.2% of controls were white; and 78.4% of target cases, 66.0% of comparison cases, and 79.2% of controls had more than a high school education.

Exposure assessment. Information on demographic factors, tobacco and alcohol use, intake of other beverages (e.g., coffee and tea), medical history, medication use, and occupational history was obtained by a structured questionnaire administered face to face by trained interviewers. Because of the high lethality of these tumours, proxy interviews (usually with a spouse or other next-of-kin) were required for 29.6% of target case participants, 32.2% of comparison case participants, and 3.4% of control participants. We analysed the data both including and excluding proxy interviews and the results were consistent (Supplementary Tables 2 and 3), and therefore we present the analysis including the proxy data. The average time between cancer diagnosis and interview for cases was 3.7 months for self-report and 8.5 months for proxy report. Interviews averaged 130 min. Written informed consent was obtained from each participant before the interview (Gammon *et al*, 1997).

Dietary data were collected by interviewers using a 104-item food frequency questionnaire (FFQ) modified from one developed and validated by investigators at the Fred Hutchinson Cancer Research Center (FHCRC) (Kristal *et al*, 1997). Participants were asked to report usual dietary intake for 3–5 years before diagnosis (case participants) or interview (control participants). Completed FFQs were not obtained for 33 participants who provided only abbreviated interviews. Estimated total energy intake of <500 or >4000 kilocalories per day for women and <800 or >5000 kilocalories per day for men were considered implausible intake values, thereby excluding 61 case and 28 control participants (Willett, 2012). Final numbers of participants included in this study were 274 with OEA, 248 with GCA, 191 with OES, and 341 with OGA cases, and 662 control participants.

Assessment of dietary flavonoid intake. A study-specific flavonoid database was created based on values from the

2011 United States Department of Agriculture (USDA) Database for the Flavonoid Content of Selected Foods (Bhagwat *et al*, 2011) and the 2008 USDA-Iowa State University Database on the Isoflavone Content of Selected Foods (Bhagwat *et al*, 2008) and supplemented with lignan content data (i.e., secoisolariciresinol and matairesinol) (Thompson *et al*, 2006). Using FFQ reported frequencies of dietary intakes, intake of total flavonoids and six classes of flavonoids (anthocyanidins, flavan-3-ols, flavanones, flavones, flavonols, and isoflavones) and lignans were estimated using the study-specific flavonoid database for 81 food and beverage items that contained measureable amounts of flavonoids (Supplementary Table 4).

When FFQ items represented groups of foods or beverages, the individual foods and beverages were weighted based on usual population consumption. For example, the FFQ item of 'apples and pears' was assigned weights of 0.75 for 'apples' and 0.25 for 'pears'. Flavonoid intake was calculated by multiplying the weight assigned to each food in the FFQ item by the flavonoid content of that food, summing across all foods in the FFQ item, and then multiplying by the number of times consumed per day. For example, 100 g of apple contains 1.29 mg and pears contain 12.18 mg of anthocyanidins. A serving size of apples or pears was estimated as 145 g. Therefore, if an individual reported consuming one serving of apples or pears per day, the individual's daily intake of anthocyanidins from apples and pears was calculated as 145 g apple or pear per day $\times$ [(0.75 apple weight $\times$ 1.29 mg per 100 g apples) + (0.25 pear weight $\times$ 12.18 mg per 100 g pear)] = 5.82 mg anthocyanidins per day.

Outcome assessment. In follow-up of the Multicenter Study, vital status and date of death were determined by linking state tumour registry data with the National Death Index. Overall survival time (in months) was calculated from the date of diagnosis until death or last follow-up, with a maximum follow-up of 90 months, ending in 2000. Median survival time was 9.6 months for the study participants diagnosed with OEA, 12.8 months for those with GCA, 10.7 months for OES, and 12.9 months for OGA. At the end of follow-up, participants who were still alive were considered censored. The outcome was death from any cause (Trivers *et al*, 2005).

Statistical analysis. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Case–control analysis. Polytomous unconditional logistic regression was used to calculate odds ratios (ORs) and their 95% confidence intervals (CIs) for the association between flavonoid/lignan intake and the risk of incidence for the four tumour types (OEA, GCA, OES, and OGA) in comparison with control participants. Effect measure modification by cigarette smoking (evaluated as ever/never and continuous duration), usual adult body mass index (BMI, evaluated as continuous and as dichotomised, <25 and $\geqslant 25\,kg\,m^{-2}$), and self-reported gastroesophageal reflux disease (yes/no) was assessed using likelihood ratio statistics to compare regression models with and without a multiplicative term (Rothman *et al*, 2008). There was no evidence for effect modification by any of these variables ($P \geqslant 0.05$) on the association between flavonoid intake and oesophageal or gastric cancer.

Potential confounders for the case–control analysis included proxy status (proxy, non-proxy), income (evaluated as $<$\$15 000, \$15 000–29 999, \$30 000–49 999, \$50 000–74 999, or $\geqslant$\$75 000 and $<$\$15 000 or $\geqslant$\$15 000), education (evaluated as $<$high school, high school, technical school/some college, or $\geqslant$college and $<$high school or $\geqslant$high school), cigarette smoking (evaluated as ever/never, continuous pack-years, and continuous cigarettes/day), alcohol consumption (evaluated as ever/never and continuous for beer, wine, and liquor), and BMI (evaluated as continuous and categorised, <25, 25–29.9, or $\geqslant 30\,kg\,m^{-2}$). If the log OR changed by $\geqslant$10% because of variable elimination, the variable was considered a confounder and remained in the model (Rothman *et al*, 2008); only cigarette smoking met this criterion. Total energy intake was included for adjustment as an *a priori* confounder (Willett *et al*, 1997). Thus, all final logistic regression models include cigarette smoking (ever/never), kilocalories (continuous), and the frequency matching factors of site (CT, NJ, and WA), age (continuous), sex (male, female), and race (white, other). Although we chose to present results adjusted utilising the standard multivariate approach for ease of interpretation, we also examined utilising the nutrient density and residual models and results did not differ (Willett, 2012) (Supplementary Table 5). Ratios of the ORs were calculated to determine heterogeneity between OEA and the other cancer subtypes.

Survival analysis. Cox proportional hazard regression analysis was used to calculate adjusted hazard ratios (HRs) and their 95% CIs for the association between flavonoid/lignan intake and mortality for each tumour type as distinct outcomes. The proportional hazards assumption was tested utilising an interaction with log(time) in models with confounders, and it was not observed to be violated.

Potential confounders for the survival analysis included the same covariates listed above in the case–control analysis, as well as study site (WA, NJ, and CT), age (continuous), sex (male, female), tumour stage (localised, regional, distant, and unknown), tumour grade (well/moderate, poor/undifferentiated, and not determined), and dysphagia (yes, no). Variables remained in the adjusted model if they were significant predictors of survival ($P<0.05$) (Rothman *et al*, 2008); only stage met this criterion. Total energy intake was included as an *a priori* confounder (Willett *et al*, 1997). Thus, all final proportional hazard models included tumour stage and kilocalories (continuous). Stratified Cox proportional hazard regression analysis, with interaction terms between cancer type and flavonoids, tumour stage, and total energy intake, was used to calculate the ratio of the HRs to determine heterogeneity between EA and the other cancer subtypes.

Examination of linear trend. Flavonoid intake was categorised as quartiles, based on the distribution of intake among the controls (logistic regression) or all cases (survival analysis) (Willett, 2012). To examine trends, we evaluated flavonoid intake with restricted quadratic splines as well as linear trends in continuous flavonoid values (mg per day).

Sensitivity analysis. For anthocyanidins, a value of 7.39 mg per 100 g of banana is assigned in the USDA Flavonoid Database (Bhagwat *et al*, 2011). However, this value is controversial (Drossard *et al*, 2011). Thus, we conducted sensitivity analyses that excluded this value (Supplementary Tables 6–9). We also stratified incidence and mortality risk estimates by tumour stage (Supplementary Tables 10 and 11).

RESULTS

As shown in Table 1, control participants consumed on average similar amounts of total flavonoids (median = 97.09 mg per day) as case participants (OEA median = 96.89; GCA median = 104.27; OES median = 108.97; OGA median = 101.32 mg per day). Flavan-3-ols were the largest contributor to total flavonoid intake in this study population, and control participants consumed less flavan-3-ols than OEA, GCA, and OGA case participants.

Table 2 lists the major sources of flavonoids and lignans in the reported food items of the control participants. For total flavonoids, black tea provided 55.8% (105.11 mg per day) of mean intake, orange/grapefruit juice 14.2% (26.75 mg per day), and wine

Table 1. Mean intakes (mg per day) of flavonoids and lignans among case and control participants, USA Multicenter Study, Connecticut, New Jersey, and Western Washington State: 1993–1995

	Controls ($N=662$)			Oesophageal adenocarcinoma ($N=274$)			Gastric cardia adenocarcinoma ($N=248$)			Oesophageal squamous cell carcinoma ($N=191$)			Other gastric adenocarcinoma ($N=341$)		
	Mean	s.d.	Range	Mean	s.d.	Range	Mean	s.d.	Range	Mean	s.d.	Range	Mean	s.d.	Range
Total flavonoids	188.31	240.76	0.77–2182.23	198.19	245.12	8.45–2199.36	219.90	270.10	5.85–1753.52	182.98	206.29	7.13–1098.55	219.20	322.57	7.05–2796.17
Anthocyanidins	14.78	11.84	0–83.18	13.34	16.60	0.09–166.59	15.50	16.31	0.41–127.54	13.51	14.88	0.12–97.54	13.32	9.78	0.42–67.98
Flavan-3-ols	121.61	229.64	0.29–2064.10	138.10	234.35	1.07–2063.16	150.53	256.87	0.68–1650.30	121.54	198.64	0.68–1037.81	154.01	307.90	0.93–2467.85
Flavanones	34.93	27.00	0–231.14	29.42[a]	24.46	0.004–125.24	35.04	24.99	0.02–113.73	29.85[a]	26.08	0–227.42	34.47	26.77	0.06–226.64
Flavones	2.07	1.16	0–7.56	2.09	1.39	0–12.50	2.26[a]	1.39	0.17–8.40	1.86[a]	1.26	0.02–6.75	2.02	1.16	0.02–8.01
Flavonols	14.46	9.41	0.36–78.60	14.70	9.68	2.22–72.82	16.04[a]	10.63	3.18–67.17	15.74	10.41	1.85–55.62	14.90	11.36	3.34–98.33
Isoflavones	0.47	0.29	0.02–2.81	0.54[a]	0.33	0.03–2.82	0.53[a]	0.31	0.07–1.99	0.49	0.27	0.05–1.67	0.49	0.28	0.03–2.24
Lignans	0.068	0.032	0.011–0.286	0.069	0.039	0.014–0.304	0.073[a]	0.036	0.016–0.247	0.061[a]	0.032	0.011–0.210	0.065	0.030	0.010–0.266
Kilocalories	2082.83	680.91	525.56–4834.74	2204.89[a]	651.26	766.62–3907.55	2210.50[a]	669.60	501.67–3946.67	2347.51[a]	707.82	530.95–3847.69	2121.50	682.85	704.36–3977.81

[a]T-test comparing the means of cases and controls, $P<0.05$.

4.5% (8.46 mg per day). Black tea was a source of flavan-3-ols, flavonols, and lignans. Orange/grapefruit juice provided flavanones, flavonols, isoflavones, and lignans. Wine was a source of anthocyanidins, flavan-3-ols, flavanones, flavones, flavonols, and lignans.

As shown in Table 3, intake of dietary anthocyanidins, for which wine, bananas, and fruit juice were the major dietary sources, was inversely associated with risk of incidence for all tumour types, although the magnitude and precision of the estimates varied by tumour type. Comparing the highest with lowest quartile of anthocyanidin intake, decreased risks were shown for incident OEA (OR = 0.43, 95% CI = 0.29–0.66, $P_{trend}=0.06$) and OES (OR = 0.43, 95% CI = 0.26–0.70, $P_{trend}=0.11$). More modest decreased risks were shown for incident GCA (OR = 0.71, 95% CI = 0.46–1.10) and OGA (OR = 0.70, 95% CI = 0.47–1.03), but the CI included the null value.

For all other flavonoid types, the associations with incident oesophageal and gastric cancers were less consistent. For example, as also shown in Table 3, dietary flavanone intake was inversely associated with incident OEA (OR = 0.56, 95% CI = 0.37–0.85, $P_{trend}=0.003$) and OES (OR = 0.48, 95% CI = 0.29–0.78, $P_{trend}=0.002$). Dietary flavone and lignan intake were inversely associated with OES incidence (OR = 0.55, 95% CI = 0.34–0.89, $P_{trend}=0.02$; OR = 0.38, 95% CI = 0.23–0.63, $P_{trend}=0.0003$, respectively). Lignan intake was more modestly associated with incident OEA (OR = 0.75, 95% CI = 0.49–1.13), but the CI included the null value.

As also shown in Table 3, we observed a modest inverse association between dietary intake of isoflavones, for which coffee, chili, and white bread were the major dietary sources, and OES incidence, but the CI included the null value; in contrast, a positive association was observed for isoflavones in relation to all other tumour types. Similarly, we observed a modest positive association for dietary flavonol intake with GCA incidence, but not other tumour types. Little or no consistent association was observed between total flavonoid intake or flavan-3-ols, accounting for 64.6% of total flavonoid intake among controls, and any tumour types.

As presented in Table 4, anthocyanidin intake was associated with a decreased risk of mortality among GCA cases (highest *vs* lowest quartile HR = 0.63, 95% CI = 0.42–0.95, $P_{trend}=0.25$) and more modestly among OEA cases (HR = 0.87, 95% CI = 0.60–1.26), which included the null value in the CI. Dietary lignan intake was associated with decreased mortality for OES cases (HR = 0.58, 95% CI = 0.37–0.92, $P_{trend}=0.07$) and more modestly for OEA cases (HR = 0.78, 95% CI = 0.54–1.14), with the CI including the null value. Flavanone intake was associated with decreased mortality for OGA cases (HR = 0.66, 95% CI = 0.46–0.93, $P_{trend}=0.18$). Flavone intake was associated with modest decreased mortality for OEA cases (HR = 0.83, 95% CI = 0.58–1.19), but the CI included the null. In addition, total flavonoid or flavonol intake was associated with little or no decreased risk of mortality for any tumour type.

A sensitivity analysis that excluded the anthocyanidin value for bananas did not substantially alter our results for oesophageal or gastric cancer incidence or survival (Supplementary Tables 6–9).

DISCUSSION

This is the first population-based study to examine associations between dietary flavonoid intake and survival among oesophageal and gastric cancer cases. In our analysis, the highest intake quartile of anthocyanidins was associated with a possible 37% and more modest 13% decreased risk of mortality for GCA and OEA cases, respectively. Lignan intake was associated with a possible 42% and more modest 22% decreased risk of mortality for OES and OEA

Table 2. Major sources of flavonoids and lignans among a population-based sample of control participants without oesophageal or gastric cancer with information on dietary intake, USA Multicenter Study: Connecticut, New Jersey, and Western Washington State, 1993–1995

Flavonoid/ phytoestrogen class	Representative flavonoids	Main FFQ line item sources (%)
Total flavonoids		Black tea (55.8), orange/grapefruit juice (14.2), wine (4.5)
Anthocyanidins	Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin	Wine (29.1), banana (13.7), fruit juice (10.6), other fruit (fruit cocktail, grapes, pineapple, blueberries, applesauce) (9.0), apples (7.5), pies (6.0), bean soup (5.9)
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 (83.7), beer (3.2), green tea (3.1), wine (2.0), apples (1.9), bananas (1.4)
Flavanones	Eriodictyol, Hesperetin, Naringenin	Orange/grapefruit juice (75.4), oranges (21.5), wine (1.8)
Flavones	Apigenin, Luteolin	Pizza (27.5), Wine (13.0), Celery (8.3), vegetable soup (7.8), mixed salad (7.8), cream soups (7.0), chicken noodle soup (5.4)
Flavonols	Isorhamnetin, Kaempferol, Myricetin, Quercetin	Black tea (22.9), onions (10.5), beer (9.2), apples (8.1), wine (5.9), mixed salad (5.9)
Isoflavones	Daidzein, Genistein, Glycitein	Coffee (36.8), chili (17.4), white bread (10.8), cake (8.4), fried chicken (5.1), sausage (4.5)
Lignans	Matairesinol, Secoisolariciresinol	Coffee (34.8), orange/grapefruit juice (13.4), wine (10.3), black tea (5.0), onions (3.5)

Abbreviation: FFQ, food frequency questionnaire.

cases, respectively. Flavanones was associated with a possible 34% decreased risk of mortality for OGA cases. We also found flavones associated with a possible 17% decreased risk of mortality for OEA cases. Although our survival results are intriguing, there are several aspects regarding our study approach (as discussed below) that should be kept in mind when interpreting our study findings.

In addition, we observed possible 25–30% risk reduction for the associations between anthocyanidins and GCA and OGA incidence and lignans and OGA incidence. We observed ~30–60% risk reductions for the associations between anthocyanidins and flavanones and OEA incidence; similar risk reductions were noted for the associations between the highest intake quartiles of anthocyanidins, flavanones, flavones, isoflavones, and lignans in relation to OES. As these four cancer types have differing risk factors (Hongo *et al*, 2009; de Martel *et al*, 2013), it is not surprising that certain flavonoids differentially influence the risk of certain subtypes of oesophageal or gastric cancer.

Our findings are consistent with a previous epidemiologic study that reported an inverse association between anthocyanidin intake and OEA incidence (Bobe *et al*, 2009). In addition, our findings regarding anthocyanidin intake are consistent with the parent (Gammon *et al*, 1997) and consortial studies (Freedman *et al*, 2011) showing a risk reduction for moderate wine intake, the main source of anthocyanidins in this study. Our results are also consistent with previous population studies regarding flavanone and isoflavone intake in relation to OES incidence (Rossi *et al*, 2007; Bobe *et al*, 2009). Previous studies, but not our study reported here, have also noted inverse associations between: flavonols and OES incidence (Rossi *et al*, 2007); flavonols (Lagiou *et al*, 2004; Rossi *et al*, 2010), flavanones (Lagiou *et al*, 2004), flavones (Lagiou *et al*, 2004), and lignans (secoisolariciresinol; Hernandez-Ramirez *et al*, 2009) and gastric adenocarcinoma (i.e., cardia and noncardia) incidence; and flavonols (quercetin) and GCA incidence (Ekstrom *et al*, 2011). Observed differences between these previous studies and our own could partially be because of considering gastric adenocarcinoma as a combined entity and not according to anatomic subsite, examining single flavonoids and not classes of flavonoids, differences in study populations and dietary patterns across studies, or chance.

In this study, notable risk reductions were observed for the associations between anthocyanidins and oesophageal cancer incidence, regardless of histologic subtype. However, in animal studies, results for anthocyanidins as chemopreventive agents are not consistent across histologic subtypes (i.e., squamous cell carcinoma *vs* adenocarcinoma). Multiple experimental studies have shown that anthocyanidin-rich black raspberries have chemopreventive properties in *N*-nitrosomethylbenzylamine-induced tumours in rats (OES rodent model) (Stoner *et al*, 2006). In a study of oesophagoduodenal anastomosis, a rodent model for reflux-induced OEA, freeze-dried black raspberries were not effective in chemoprevention of OEA (Aiyer *et al*, 2011). However, interim clinical trial results for Barrett's oesophagus, a potential precursor of OEA, found reduced markers of oxidative stress in Barrett's oesophagus patients consuming anthocyanidin-rich freeze-dried black raspberries (Kresty *et al*, 2006).

A previous study, based on data from the same parent study as our own, found a modest inverse association between fruit and vegetable intake and incidence of both histologic subtypes of oesophageal cancer (Navarro Silvera *et al*, 2008). As flavonoids are concentrated in fruits and vegetables (D'Archivio *et al*, 2007), the association between flavonoids and oesophageal or gastric cancer incidence may reflect diets with greater consumption of such foods or a healthy lifestyle in general. The parent study assessed many lifestyle factors, including cigarette smoking, alcohol intake, and BMI, individually (Gammon *et al*, 1997) and through the use of pattern analyses (Navarro Silvera *et al*, 2008). Cigarette smoking was the only covariate among these that influenced our findings and was adjusted for in the final models. Thus, lifestyle seems unlikely to account for our results.

When estimating flavonoid content in food, particularly fruits and vegetables, potential sources of error include plant varieties, degree of ripeness, storage conditions, distance transported to market, environmental factors affecting plant growth, horticultural practices, industrial processing, and cooking methods that may vary over time and by geographic region (D'Archivio *et al*, 2007). Therefore, the foods utilised to create the nutrient database

Table 3. Adjusted[a] odds ratios (ORs) and 95% confidence intervals (CIs) for associations between flavonoid and lignan intakes and oesophageal and gastric cancer incidence by tumour type, USA Multicenter Study: Connecticut, New Jersey, and Western Washington State, 1993–1995

		Oesophageal adenocarcinoma (OEA)		Gastric cardia adenocarcinoma (GCA)		Oesophageal squamous cell carcinoma (OES)		Other gastric adenocarcinoma (OGA)	
Variable and intake (mg per day)	Controls (*N* = 662)	Cases (*N* = 274)	OR (95% CI)	Cases (*N* = 248)	OR (95% CI)	Cases (*N* = 191)	OR (95% CI)	Cases (*N* = 341)	OR (95% CI)
Total flavonoids									
0–63.81	165	83	1.00	59	1.00	48	1.00	80	1.00
63.82–97.90	166	54	0.62 (0.41, 0.93)[b,c]	60	1.00 (0.65, 1.54)	35	0.64 (0.38, 1.07)[b]	84	1.01 (0.69, 1.49)[c]
97.91–217.35	165	57	0.64 (0.42, 0.97)	54	0.90 (0.58, 1.41)	61	1.11 (0.69, 1.77)	78	0.92 (0.62, 1.37)
⩾217.36	166	80	0.92 (0.63, 1.37)	75	1.32 (0.87, 2.00)	47	0.87 (0.53, 1.41)	99	1.08 (0.73, 1.58)
P for trend[d]			0.61		0.07		0.42		0.50
Anthocyanidins									
0–7.21	166	98	1.00	67	1.00	67	1.00	92	1.00
7.22–11.53	165	69	0.65 (0.45, 0.96)	67	0.98 (0.65, 1.47)	51	0.68 (0.43, 1.06)	89	0.91 (0.63, 1.32)
11.54–18.47	165	59	0.54 (0.36, 0.81)[c,e]	63	0.91 (0.60, 1.38)[e]	37	0.44 (0.27, 0.72)	91	0.89 (0.61, 1.29)[c]
⩾18.48	166	48	0.43 (0.29, 0.66)	51	0.71 (0.46, 1.10)	36	0.43 (0.26, 0.70)	69	0.70 (0.47, 1.03)
P for trend[d]			0.06[c,e]		0.91[e]		0.11		0.10[c]
Flavan-3-ols									
0–10.29	165	75	1.00	59	1.00	45	1.00	71	1.00
10.30–22.00	166	61	0.72 (0.48, 1.09)[c]	50	0.77 (0.50, 1.20)	37	0.78 (0.47, 1.30)	101	1.45 (0.99, 2.14)[c]
22.01–130.69	165	56	0.65 (0.43, 1.00)	69	1.05 (0.69, 1.61)	62	1.24 (0.77, 2.00)	68	0.98 (0.65, 1.48)
⩾130.70	166	82	1.02 (0.69, 1.51)	70	1.17 (0.77, 1.78)	47	0.98 (0.60, 1.59)	101	1.30 (0.88, 1.92)
P for trend[d]			0.32		0.07		0.68		0.36
Flavanones									
0–11.57	166	91	1.00	62	1.00	61	1.00	89	1.00
11.58–34.95	165	61	0.67 (0.45, 1.00)	54	0.86 (0.56, 1.33)	45	0.70 (0.44, 1.11)	80	0.92 (0.63, 1.35)
34.96–49.52	165	69	0.75 (0.50, 1.10)	59	1.01 (0.66, 1.55)	49	0.69 (0.43, 1.10)	83	0.86 (0.59, 1.27)
⩾49.53	166	53	0.56 (0.37, 0.85)[e]	73	1.23 (0.81, 1.87)[e]	36	0.48 (0.29, 0.78)	89	0.88 (0.60, 1.28)
P for trend[d]			0.003[e]		0.82[e]		0.002		0.36
Flavones									
0–1.29	165	82	1.00	60	1.00	71	1.00	95	1.00
1.30–1.90	166	58	0.67 (0.45, 1.00)	55	0.87 (0.57, 1.34)	51	0.70 (0.45, 1.09)	87	0.92 (0.64, 1.34)
1.91–2.62	166	59	0.68 (0.45, 1.02)[b]	62	0.98 (0.64, 1.50)	28	0.34 (0.20, 0.57)[b]	72	0.77 (0.52, 1.13)
⩾2.63	165	75	0.84 (0.56, 1.25)	71	1.09 (0.71, 1.67)	41	0.55 (0.34, 0.89)	87	1.01 (0.69, 1.50)
P for trend[d]			0.81[b]		0.15		0.02[b]		0.98
Flavonols									
0–8.31	166	86	1.00	52	1.00	56	1.00	82	1.00
8.32–12.16	165	49	0.56 (0.37, 0.85)[e,f]	64	1.24 (0.81, 1.91)[e]	33	0.59 (0.36, 0.98)	94	1.16 (0.80, 1.69)[c]
12.17–17.81	166	61	0.67 (0.45, 1.00)	53	1.01 (0.65, 1.57)	39	0.70 (0.43, 1.14)	79	0.96 (0.65, 1.41)
⩾17.82	165	78	0.80 (0.54, 1.18)[e]	79	1.42 (0.93, 2.17)[e]	63	0.97 (0.62, 1.53)	86	0.98 (0.67, 1.46)
P for trend[d]			0.71		0.10		0.70		0.92
Isoflavones									
0–0.27	165	47	1.00	36	1.00	34	1.00	65	1.00
0.28–0.41	166	51	0.98 (0.61, 1.55)	64	1.55 (0.97, 2.49)	50	1.12 (0.67, 1.89)	90	1.45 (0.97, 2.17)
0.42–0.59	166	83	1.51 (0.97, 2.37)	73	1.62 (1.00, 2.63)	59	1.18 (0.69, 2.00)	97	1.68 (1.10, 2.56)
⩾0.60	165	93	1.65 (1.02, 2.65)[b]	75	1.56 (0.93, 2.60)	48	0.72 (0.40, 1.29)[b]	89	1.50 (0.96, 2.37)
P for trend[d]			0.07[b]		0.17		0.11[b]		0.37
Lignans									
0–0.045	165	70	1.00	50	1.00	67	1.00	87	1.00
0.046–0.063	166	75	0.91 (0.61, 1.36)	61	1.06 (0.69, 1.65)	47	0.64 (0.40, 1.01)	92	1.09 (0.75, 1.59)
0.064–0.082	165	57	0.65 (0.42, 0.99)[c,e]	70	1.17 (0.76, 1.81)[e]	42	0.50 (0.31, 0.82)	98	1.11 (0.76, 1.63)[c]
⩾0.083	166	72	0.75 (0.49, 1.13)[b]	67	1.01 (0.65, 1.58)	35	0.38 (0.23, 0.63)[b]	64	0.73 (0.48, 1.11)
P for trend[d]			0.26[b]		0.63		0.0003[b]		0.13

[a]Adjusted for age (continuous), sex, race (white, other), geographic centre (Connecticut, New Jersey, Washington), cigarette smoking (ever/never), and dietary energy intake (kilocalories, continuous).
[b]*P*-value <0.05 for the ratio of the odds ratios comparing OEA *vs* OES.
[c]*P*-value <0.05 for the ratio of the odds ratios comparing OEA *vs* OGA.
[d]*P*-value for trend for continuous variable.
[e]*P*-value <0.05 for the ratio of the odds ratios comparing OEA *vs* GCA.

estimates may differ from the actual food sources reportedly consumed by this study population (Thompson *et al*, 2006; Bhagwat *et al*, 2008, 2011). To estimate the potential impact of such influences, the USDA Food Composition and Nutrient Data Laboratories sampled over 60 fruits, vegetables, and nuts from four USA regions at two times of the year and estimated the flavonoid content. Values reported in the USDA databases were similar to average flavonoid content determined in this study, although high variability of flavonoid content was seen within and between foods (Harnly *et al*, 2006). In addition, the FFQ line item for wine did not distinguish between red and white that have different flavonoid concentrations (Bhagwat *et al*, 2011). In our study reported here, weights of 50% for red and 50% for white were assigned. However, individuals often preferentially drink red or white wine, and thus individual estimates of flavonoid types for which wine is a source may be misclassified.

Bioavailability of flavonoid compounds is another potential source of error when estimating the amount of flavonoid intake necessary to reduce risk of oesophageal or gastric cancer. However, little is known about flavonoid absorption in the gastrointestinal tract, metabolism of flavonoids varies by individual, and the degree to which flavonoids might have direct effects on epithelial surfaces

Table 4. Adjusted[a] hazard ratios (HRs) and 95% confidence intervals (CIs) for flavonoid and lignan intakes and overall mortality in oesophageal or gastric cancer cases by tumour type, USA Multicenter Study: Connecticut, New Jersey, and Western Washington State, 1993–1995

	Oesophageal adenocarcinoma (OEA)		Gastric cardia adenocarcinoma (GCA)		Oesophageal squamous cell carcinoma (OES)		Other gastric adenocarcinoma (OGA)	
Variable and intake (mg per day)	Cases (*N* = 274)	HR (95% CI)	Cases (*N* = 248)	HR (95% CI)	Cases (*N* = 191)	HR (95% CI)	Cases (*N* = 338)	HR (95% CI)
Total flavonoids								
0–62.35	83	1.00	57	1.00	47	1.00	76	1.00
62.36–103.39	60	1.37 (0.95, 1.98)	66	1.05 (0.71, 1.54)	42	1.26 (0.81, 1.97)	95	1.01 (0.71, 1.42)
103.40–253.24	65	1.39 (0.97, 1.98)[b,c]	60	0.79 (0.54, 1.17)[b]	61	0.92 (0.60, 1.40)	77	0.72 (0.50, 1.05)[c]
⩾253.25	66	0.98 (0.68, 1.41)	65	0.88 (0.59, 1.32)	41	0.91 (0.58, 1.44)	90	0.99 (0.70, 1.39)
P for trend[d]		0.11		0.80		0.11		0.90
Anthocyanidins								
0–6.23	83	1.00	52	1.00	57	1.00	70	1.00
6.24–10.11	61	0.93 (0.65, 1.35)	64	0.76 (0.51, 1.12)	52	0.77 (0.50, 1.18)	86	1.27 (0.89, 1.82)
10.12–16.23	67	0.88 (0.62, 1.26)	66	0.80 (0.54, 1.18)	41	1.46 (0.94, 2.26)	89	1.22 (0.84, 1.76)
⩾16.24	63	0.87 (0.60, 1.26)	66	0.63 (0.42, 0.95)	41	1.01 (0.66, 1.56)	93	1.14 (0.80, 1.63)
P for trend[d]		0.14		0.25		0.94		0.55
Flavan-3-ols								
0–10.90	80	1.00	61	1.00	47	1.00	75	1.00
10.91–26.67	62	0.92 (0.64, 1.32)	53	0.69 (0.46, 1.04)	46	1.68 (1.08, 2.62)	102	1.33 (0.94, 1.87)
26.68–210.51	66	1.20 (0.84, 1.72)[e]	71	0.78 (0.54, 1.13)	56	0.97 (0.63, 1.50)[e]	70	0.96 (0.66, 1.39)
⩾210.52	66	0.93 (0.65, 1.33)	63	0.71 (0.48, 1.05)	42	1.09 (0.69, 1.74)	91	1.22 (0.87, 1.73)
P for trend[d]		0.11		0.94		0.10		0.80
Flavanones								
0–8.63	81	1.00	55	1.00	50	1.00	77	1.00
8.64–32.94	66	0.96 (0.67, 1.38)	60	1.12 (0.75, 1.69)	54	0.95 (0.61, 1.47)	83	0.70 (0.49, 1.00)
34.95–49.00	71	1.40 (0.99, 1.98)[c]	57	1.24 (0.83, 1.86)	48	1.05 (0.67, 1.63)	87	0.74 (0.52, 1.05)[c]
⩾49.01	56	1.15 (0.79, 1.68)[c]	76	0.90 (0.61, 1.33)	39	1.24 (0.76, 2.03)	91	0.66 (0.46, 0.93)[c]
P for trend[d]		0.05[c]		0.50		0.80		0.18[c]
Flavones								
0–1.20	79	1.00	46	1.00	64	1.00	74	1.00
1.21–1.81	52	0.97 (0.66, 1.41)	63	1.03 (0.68, 1.56)	48	1.23 (0.82, 1.84)	100	0.88 (0.63, 1.24)
1.82–2.64	73	0.89 (0.63, 1.26)	70	0.95 (0.63, 1.44)	39	0.88 (0.56, 1.38)	80	0.88 (0.61, 1.26)
⩾2.65	70	0.83 (0.58, 1.19)	69	0.86 (0.56, 1.31)	40	1.00 (0.64, 1.54)	84	0.97 (0.67, 1.39)
P for trend[d]		0.04		0.54		0.17		0.62
Flavonols								
0–8.16	79	1.00	50	1.00	55	1.00	79	1.00
8.17–12.30	60	1.30 (0.89, 1.89)	68	1.25 (0.83, 1.87)	36	1.14 (0.70, 1.83)	98	1.12 (0.80, 1.57)
12.31–19.34	72	1.01 (0.71, 1.43)	63	1.11 (0.74, 1.68)	45	0.78 (0.50, 1.20)	84	1.09 (0.78, 1.54)
⩾19.35	63	0.94 (0.65, 1.37)	67	0.93 (0.61, 1.40)	55	0.93 (0.61, 1.40)	77	0.97 (0.68, 1.38)
P for trend[d]		0.05		0.35		0.69		0.71
Isoflavones								
0–0.31	65	1.00	59	1.00	48	1.00	89	1.00
0.32–0.46	56	1.00 (0.68, 1.47)	57	1.26 (0.84, 1.87)	60	1.03 (0.68, 1.58)	90	1.29 (0.92, 1.82)
0.47–0.62	73	0.70 (0.48, 1.03)	68	0.94 (0.62, 1.44)	42	1.14 (0.71, 1.81)	81	0.86 (0.60, 1.25)
⩾0.63	80	0.75 (0.49, 1.13)	64	1.01 (0.65, 1.57)	41	0.97 (0.60, 1.58)	78	0.92 (0.62, 1.37)
P for trend[d]		0.65		0.77		0.60		0.88
Lignans								
0–0.044	68	1.00	50	1.00	62	1.00	83	1.00
0.045–0.060	72	0.85 (0.60, 1.23)	55	1.45 (0.95, 2.22)	50	0.73 (0.47, 1.13)	85	1.22 (0.86, 1.73)
0.061–0.079	57	0.98 (0.67, 1.45)	66	1.05 (0.70, 1.59)	41	0.61 (0.39, 0.96)	99	1.08 (0.77, 1.51)
⩾0.080	77	0.78 (0.54, 1.14)	77	0.97 (0.65, 1.46)	38	0.58 (0.37, 0.92)	71	1.05 (0.72, 1.53)
P for trend[d]		0.28		0.43		0.07		0.55

[a]Adjusted for stage (localised, regional, distant, unknown) and dietary energy intake (kilocalories, continuous).
[b]*P*-value <0.05 for the ratio of the hazard ratios comparing OEA *vs* GCA.
[c]*P*-value <0.05 for the ratio of the hazard ratios comparing OEA *vs* OGA.
[d]*P*-value for trend for continuous variable.
[e]*P*-value <0.05 for the ratio of the hazard ratios comparing OEA *vs* OES.

as they traverse the oesophagus and stomach is unclear (Bravo, 1998). In addition, absorption profiles of flavonoids vary, with maximum concentrations reached between 0.5 and 9 h after dietary intake (Spencer *et al*, 2008). Thus, serum flavonoid biomarkers may not be highly correlated with usual adult dietary intake. Although such variation in estimating representative dietary flavonoid intakes and bioavailability may be a study limitation, this issue would apply to greater or lesser degrees to all studies reliant on nutritional databases to estimate dietary intake (Willett, 2012).

Patients with gastroesophageal reflux disease or Barrett's oesophagus are recommended to omit foods that are mechanically or chemically irritating, including some flavonoid-rich foods

(e.g., coffee, tea, alcohol, citrus, tomatoes, chocolate, peppers, and onions) (Ko *et al*, 2008). Although the FFQ assessed diet before diagnosis, OEA patients may already have symptoms before diagnosis, causing their usual diet to change or, perhaps, reporting of past diet could be influenced by current dietary habits. However, the foods that are irritating vary by individual (Brown, 2008); thus, we are unable to estimate how such potential changes in diet would have affected flavonoid intake values. In addition, a dietary study showed that intakes of fruits, vegetables, and alcohol did not differ by symptomatic gastroesophageal reflux disease status (El-Serag *et al*, 2005). Although it is unknown whether gastroesophageal reflux disease or Barrett's oesophagus are necessary precursors of OEA (Shaheen and Ransohoff, 2002), it is still possible that associations observed in case–control studies between flavonoid intake and risk of OEA are due to reverse causation. However, in examining the comparison case group of OES, we see similar associations, with the exception of isoflavones. Thus, it seems unlikely that our observed associations are completely because of reverse causation.

Although our observed association with oesophageal and gastric cancers could possibly reflect a true association with select flavonoid classes, or perhaps a healthy prediagnostic behaviour lifestyle in general, there are additional measurement issues to consider during the interpretation of our findings. For example, FFQ responses for the 3–5 years before diagnosis are assumed to reflect usual adult diet, both pre- and post-diagnosis. Whether such time period reflects intakes during the time relevant to oesophageal and gastric cancer development is unknown. However, because all existing oesophageal and gastric cancer studies have relied on FFQs (Lunet *et al*, 2007; Li *et al*, 2014), one would need to conduct a cohort study and employ multiple alternative dietary assessment methods over time to overcome limitations of existing studies. Such an alternative study design would be very inefficient, because the lifetime risk of oesophageal or gastric cancer in the general United States population is $<1\%$ (Howlader *et al*). Similarly for the survival analyses, potential changes in dietary intake after diagnosis may be a relevant exposure but we were not able to assess this from available data.

Our study FFQ did not assess dietary supplement use of flavonoids. However, it is unlikely that use of flavonoid-rich supplements was widespread during this study time period, as flavonoid supplements were not patented in the United States until after completion of participant interviews in our parent study (U.S. Patent Office). In addition, we were unable to assess post-diagnosis medications or first course of treatment that may confound the survival analyses. Finally, the majority of participants were Caucasian males with low socioeconomic status. The overwhelming majority of individuals who develop oesophageal and gastric cancer are Caucasian males (Falk, 2009). Thus, the results are still largely generalisable to those at highest risk of developing these deadly cancers.

Multiple comparisons need to be considered when discussing the study results, as there were 64 comparisons within the main analyses, given we considered 8 exposures and 8 outcomes. Thus, there is a possibility that some statistically significant results arose because of chance. Adjusting for multiple comparisons would reduce the likelihood of detecting a false positive association, but would reduce power for detecting a true association if one exists. Instead, we chose to focus on associations based on biologic plausibility and consistency with published results (Rothman, 1990; Willett, 2012); we also gave more credence to results that were consistent across the continuum of cancer development. For example, in this study, we noted inverse associations for both incidence and survival for OEA in relation to anthocyanidin intake.

In summary, our population-based findings suggest that dietary intake of some types of flavonoids, particularly anthocyanidins, may lower the risk of oesophageal and gastric cancer incidence and may potentially enhance survival. This is the first epidemiologic study to examine the association of flavonoids and lignans with survival among oesophageal and gastric cancer cases, and one of few studies to examine these compounds in associations with the risk of incident oesophageal and gastric cancer by tumour type. Our findings here on anthocyanidins are consistent for incidence and survival of OEA and GCA, suggesting that these compounds could perhaps potentially be used in an effort to reduce mortality because of these fatal cancers. However, further research is needed before definite conclusions can be made about the chemopreventive role of dietary flavonoids and lignans on oesophageal and gastric cancer incidence and survival.

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CONFLICT OF INTEREST

PEA participated in this research during predoctoral work at UNC-Chapel Hill and currently consults for various pharmaceutical companies. No money was received from any pharmaceutical company. The remaining authors declare no conflict of interest.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Certain data used in this study were obtained from the Connecticut Tumor Registry, located in the Connecticut Department of Public Health. The authors assume full responsibility for analyses and interpretation of these data.

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