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Flavonoid consumption and esophageal cancer among black and white men in the United States

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Abstract

Flavonoids and proanthocyanidins are bioactive polyphenolic components of fruits and vegetables that may account for part of the protective effect of raw fruit and vegetable consumption in esophageal cancer. We studied the relationship between esophageal cancer and dietary proanthocyanidins, flavonoids and flavonoid subclasses (anthocyanidins, flavan-3-ols, flavanones, flavones, flavonols and isoflavonoids) using recently developed USDA and Tufts flavonoid and proanthocyanidin databases. The study was a population-based, case–control analysis of 161 white men with esophageal adenocarcinoma (EAC), 114 white and 218 black men with esophageal squamous cell carcinoma (ESCC) and 678 white and 557 black male controls who lived in 3 areas of the United States. Neither total flavonoid nor proanthocyanidin intake was associated with EAC and ESCC in either white or black men. In white men, inverse associations were observed between anthocyanidin intake and EAC (4th *vs.* 1st quartile odds ratio [OR], 0.47, 95% confidence interval [CI], 0.24–0.91; $p_{trend} = 0.04$) and between isoflavonoid intake and ESCC (4th *vs.* 1st quartile OR, 0.43, 95% CI, 0.20–0.93; $p_{trend} = 0.01$). None of the associations remained significant after adjusting for dietary fiber, which is strongly correlated with flavonoid consumption. We conclude

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that total flavonoids and proanthocyanidins do not have strong protective effects in either EAC or ESCC. Some protective effects were evident in flavonoid subclasses and population subgroups. In white men, foods rich in anthocyanidins may have chemopreventive effects in EAC and those rich in isoflavonoids may do so in ESCC.

Keywords

case–control study; esophageal adenocarcinoma; esophageal squamous cell carcinoma; flavonoids; proanthocyanidins

Low raw fruit and vegetable consumption has been associated with increased risk of the 2 primary histological subtypes of esophageal cancer, esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC), in both case-control and prospective cohort studies.[1] A population-based case-control study of EAC and ESCC among black and white men in the United States also suggested that these effects might differ between histological subtypes, population subgroups and food groups.[2,3] Flavonoids and proanthocyanidins (condensed tannins) are a group of bioactive polyphenols that are present in raw fruits and vegetables such as citrus fruits, apples and legumes as well as in beverages such as tea, citrus fruit juices and wine.[4,5] They might partially account for the protective effect of high raw fruit and vegetable consumption in EAC and ESCC. The plant sources of the 6 major classes of dietary monomeric flavonoids, such as anthocyanidins, flavan-3-ols (catechins), flavanones, flavones, flavonols and isoflavonoids, differ as do those for proanthocyanidins, oligomers and polymers of flavan-3-ol units.[6] Monomeric flavonoids and proanthocyanidins have anticarcinogenic properties, including antioxidative, antimutagenic, antiinflammatory and antiproliferative effects, that vary in their mechanism of action, site and strength from 1 compound to another.[7,8]

The lack of comprehensive flavonoid and proanthocyanidin databases for foods[9] has limited epidemiological investigations of their role in esophageal cancer prevention to only 3 case–control studies.[10–12] Total flavonoid consumption was inversely associated with esophageal cancer in 1 study[11] but was not associated with ESCC in another.[10] Of 5 major dietary flavonoid classes, only flavanone consumption was inversely associated with ESCC.[10] No association was observed between urinary flavan-3-ols from tea and esophageal cancer.[12] The effect of flavonoid consumption on EAC and the effect of isoflavonoid and proanthocyanidin consumption on any type of esophageal cancer have not been reported. To examine the association between flavonoid and proanthocyanidin intake and EAC and ESCC, we developed a flavonoid and proanthocyanidin database especially for our study. Dietary, beverage and other risk factor data were collected using a population-based, case–control study of 161 white men with EAC, 114 white men with ESCC, 218 black men with ESCC and 678 white and 557 black controls living in 3 areas of the United States.[2,3]

Material and methods

Study design and population

Our study was part of a concurrent population-based, multicenter, case–control interview study that examined risk factors for 4 cancers that occur in excess among blacks (esophageal, prostate, pancreatic cancer and multiple myeloma).[2,3] It was conducted in 3 areas of the U.S.: Atlanta (deKalb and Fulton counties), Detroit (Macomb, Oakland and Wayne counties) and New Jersey (Atlantic, Burlington, Camden, Essex, Hudson, Mercer, Middlesex, Monmouth, Passaic and Union counties). For the current study, white and black male residents, aged 30–79 years, were eligible if they were newly diagnosed (between August 1, 1986 and April 30, 1989) with histologically confirmed esophageal cancer (International Classification of Disease for Oncology ICD-O, 1976, site code 150) or cancer of the esophagogastric junction (ICD-O site code 151.0). Cases were identified from pathology and outpatient records at hospitals in the catchment areas. The median number of days between date of diagnosis and interview was 49. Controls were selected to be similar to the expected age (5-year age groups), race and geographic distribution of the cases using a random-digit dialing method for those aged 30–64 years and computerized listings of Medicare registrants provided by the Health Care Financing Administration (now called the Centers for Medicare & Medicaid Services) for those aged 65–79. Controls were excluded if they had a prior incidence of any of the 4 cancer types. History of digestive diseases was not an exclusion criterium. A single large control group was selected for all 4 cancer types, which resulted in some differences in age and area distribution between ESCC and EAC cases and controls.

Diet and lifestyle data

Trained interviewers conducted in-person interviews in the homes of the participants lasting ~60 min. Detailed information was obtained on sociodemographic factors, use of alcohol, coffee, tea and tobacco, usual occupation, medical and dental history and usual adult diet. Information was collected on some gastrointestinal diseases, such as history of duodenal or stomach ulcers (14.2% of white controls, 23.0% of white EAC cases, 14.0% of white ESCC cases, 14.4% of black controls and 11.0% of black ESCC cases) and among controls for history of pancreatitis (1.2% of white controls and 1.1% of black controls) and gallbladder removal (7.7% of white controls and 1.3% of black controls). Information was not collected on Barrett’s esophagus, a premalignant lesion of EAC, or medical conditions related to Barrett’s esophagus, such as gastroesophageal reflux disease and hiatal hernia or Helicobacter pylori status. Interviews were completed for 68% of the cases and 76% of the controls with proportions similar for white and black men. Reasons for nonresponse included death (19% cases; 1% controls), illness (8% cases, 4% controls) and refusal (4% cases, 16% controls). No proxy interviews with next of kin were conducted.

A detailed description of the dietary assessment methodology is provided elsewhere.[13] Briefly, participants were asked to recall their usual consumption frequency, excluding the last 5 years, of 57 specific food items (*e.g.*, cauliflower, green peas, bananas, chicken) or groups of similar foods (*e.g.*, spaghetti, macaroni or noodles) and 18 questions on beverage consumption (*e.g.*, fruit juices). Nutrient intakes were estimated based on the frequency of

consumption of each food and beverage item and the nutrient content of an average serving for males obtained from the National Health and Nutrition Examination Survey nutrient data base.[14] Participants were also asked about their use of vitamin supplements 5 years before the interview and their usual adult weight and height. We excluded 13 (6.9%) EAC cases, 10 (8.1%) white and 31 (12.4%) black ESCC cases and 72 (9.6%) white and 57 (9.1%) black controls because they had missing data on smoking, alcohol use, weight, height, incomplete dietary data or reported extremely high or low values for total amount of food consumed. We also excluded black EAC cases, because the number of black EAC cases ($n = 10$) was too small for a meaningful statistical analysis. The final analysis was based on 161 white patients diagnosed with EAC (ICD-O site codes 150 and 151.0 histological codes 8140-8573), 114 white and 218 black patients diagnosed with ESCC (ICD-O site code 150 histological codes 8050-8082) and 678 white and 557 black controls.

Flavonoid and proanthocyanidin intakes

A total of 55 food and beverage items contributed to flavonoid estimates and 23 items to the proanthocyanidin estimate. The flavonoid and proanthocyanidin database for the interview questionnaire was developed by one of us (J.P.) based on USDA and Tufts flavonoid and proanthocyanidin databases for food.[15] Primarily, intakes of flavonoids were estimated from the 2007 USDA flavonoid database for 394 food items,[16] isoflavonoid intakes from the 2007 USDA-Iowa State University isoflavonoid database for foods[17] and proanthocyanidin intakes from the 2004 USDA proanthocyanidin database.[18] When values for a processed food item were missing, 50% of the raw food values were used to account for possible losses of flavonoids and proanthocyanidins during food preparation. Total flavonoid intake was calculated from the sum of the 6 flavonoid subclasses. Anthocyanidins were calculated as the sum of cyanidin, delphinidin, malvidin, pelargonidin, peonidin and petunidin; flavan-3-ols as the sum of (−)-epicatechin, (−)-epicatechin 3-gallate, (−)-epigallocatechin, (−)-epigallocatechin 3-gallate, (+)-catechin and (+)-gallocatechin; flavanones as the sum of eriodictyol, hesperetin and naringenin; flavones as the sum of acacetin, apigenin, chrysieriol, diosmetin, isosinensetin, luteolin, nobiletin, sinensetin, tangeretin and tetra-*O*-methylscutellarein; flavonols as the sum of isorhamnetin, kaempferol, myricetin and quercetin and isoflavonoids as the sum of coumesterol, daidzein, genistein, formononetin and biochanin A. Proanthocyanidin intakes were calculated as the sum of the monomers, dimers, trimers, 4–6 oligomers, 7–10 oligomers and polymers (>10) of flavan-3-ol units.

Statistical analyses

Statistical analyses were performed using Statistical Analysis Systems, version 9.1 (SAS, Cary, NC) software. We tested differences between population subgroups with χ^2-tests for categorical variables and the Wilcoxon rank-sum test for continuous variables. Differences in flavonoid and proanthocyanidin values were tested for both their raw and energy-adjusted values by nutrient density (mg/1,000 kcal) and by the residual method.[19] We calculated the mean food and beverage sources for the flavonoid and proanthocyanidin intake from both total and nonalcohol sources of each study group (*i.e.*, white controls, white EAC cases, white ESCC cases, black controls and black ESCC cases). The associations among flavonoid subclasses, proanthocyanidins, flavonoid-rich foods and other nutrients were estimated using Spearman rank correlation coefficients. Unconditional logistic regression was used to

calculate odds ratios (OR) and 95% confidence intervals (95% CI) between the higher *versus* the lowest intake quartile in mg/1,000 kcal and esophageal cancer. The median intake of each quartile was used as a continuous score variable to determine the p value for trend (p_{trend}). The intakes in mg/1,000 kcal of each participant were used as a linear covariate to calculate continuous OR. Differences were considered to be significant at $p < 0.05$.

Multivariate-adjusted logistic regression models included smoking duration (0, <30, 30–39, ≥40 years) and intensity (0, <20, 20–39, ≥40 cigarettes/day), area (Atlanta, Detroit, New Jersey), age (<50, 50–59, 60–69, ≥70 years), body mass index (<25.0, 25.0–29.9, ≥30 kg/m^2), hot tea consumption (0, <1, 1–2, >2 20 oz cups of hot tea/day), hard liquor consumption (0, <1, 1–2, 2–4, >4 1.5 oz drinks of liquor/day), beer consumption (0, ≤1, 1–2, 2–4, >4 12oz drinks of beer/day), moonshine consumption (only for black men: 0, ≤1, >1 1.5 oz drinks of moonshine/day), red wine consumption (for black men and for EAC in white men: 0, <1, 1–2, >2 4 oz glasses of red wine/day; for ESCC in white men: 0, ≤1, >1 4 oz glasses of red wine/day), white wine consumption (only for EAC and ESCC in black men: 0, ≤1, >1 4 oz glasses of white wine/day), caloric intake (for white men: <1,403, 1,403–1,787, 1,788–2,146, ≥2,146 kcal/day; for black men: <1,348, 1,348–1,731, 1,732–2,260, ≤2,260 kcal/day), education (only for black men: <high school, high school, >high school) and income (for white men: <$10,000, $10,000–24,999, $25,000–49,999, ≥$50,000/year, no answer provided; for black men: <$10,000, $10,000–24,999, ≥$25,000/year, no answer provided). Inclusion of marital status or history of ulcer did not further improve the fit of the models for any comparison. Inclusion of education improved the fit for ESCC in black men but not for EAC or ESCC in white men.

Prespecified dietary variables evaluated as potential confounders were consumption of raw fruits, raw vegetables, raw fruits and vegetables, cruciferous vegetables, red meats, preserved meats, dietary fiber, vitamin C and use of multivitamins. In our study population, these dietary variables were associated with altered risk of EAC or ESCC.[2,3] Dietary variables were considered confounders if they were associated with both risk of EAC or ESCC and consumption of flavonoids and proanthocyanidins, had a χ^2 p value ≤0.20 and changed the OR by more than 10%. We also evaluated the effect modification by alcohol use (≤2 *vs.* >2 alcoholic drinks/day) and smoking intensity (<20 *vs.* ≥20 cigarettes/day).

Results

Flavonoid and proanthocyanidin intake and EAC in white men

White EAC cases smoked more and longer, drank more alcohol, had a greater dietary energy intake, weighed more, were older and had lower incomes than white controls (Table I). White EAC cases and controls did not differ significantly in their daily intake of total flavonoids, flavonoid subgroups and proanthocyanidins (Table II). Energy-adjusted (by both residual and nutrient density methods) consumption of total anthocyanidins and anthocyandins from nonalcohol sources was lower in white EAC cases (data not shown). The mean proportions of flavonoids and proanthocyanidins from alcoholic beverages for white EAC cases were as follows: total flavonoids (16.2%), proanthocyanidins (7.1%), anthocyanidins (33.9%), flavan-3-ols (19.6%), flavanones (2.2%), flavones (5.1%) and flavonols (22.4%). The main dietary sources of anthocyanidins (>5% of daily intake) in

white controls were bananas, red wine, raw apples or pears and peas other than green peas (Table III), of which bananas ($p = 0.06$) and peas ($p = 0.08$) tended to be lower in white EAC cases than in white controls.

The only significant inverse relationship with EAC risk was observed for high vs. low consumption of total anthocyanidins (OR, 0.47, 95% CI, 0.24–0.91; $p_{trend} = 0.04$; Table IV; continuous OR per mg/1,000 kcal increase, 0.89, 95% CI, 0.81–0.96) and anthocyanidins from nonalcohol sources (OR, 0.40, 95% CI, 0.22–0.75; $p_{trend} = 0.004$; continuous OR, 0.82, 95% CI, 0.73–0.93; data not shown). Adjusting for consumption of vitamin C, raw vegetables, red meats or preserved meats did not change the OR by more than 10%. No significant effect modification was observed by smoking or drinking intensity between EAC risk and consumption of total flavonoids, proanthocyanidins or flavonoid subclasses, respectively.

Anthocyanidin consumption was correlated strongly with consumption of dietary fiber (0.61), raw fruits and vegetables (0.63) and raw fruits (0.71) and less strongly with cruciferous vegetables (0.31). The associations between anthocyanidin consumption and EAC attenuated after including consumption of fiber, raw fruits and vegetables, raw fruits or cruciferous vegetables into the model and *vice versa*. For example, the ORs for high vs. low anthocyanidin consumption and EAC risk were for total anthocyanidins OR, 0.70, 95% CI, 0.33–1.48; continuous OR, 0.90, 95% CI, 0.83–0.98 and for anthocyanidins from nonalcohol sources OR, 0.55, 95% CI, 0.28–1.08; continuous OR, 0.84, 95% CI, 0.73–0.96 after adjusting for dietary fiber. Adjusting for fiber and anthocyanidin consumption additively attenuated the risk estimates in white men with EAC for high *vs.* low raw fruit and vegetable consumption from OR, 0.48, 95% CI, 0.26–0.90 to OR, 0.96, 95% CI, 0.40–2.30.

Flavonoid and proanthocyanidin intake and ESCC in white men

White ESCC cases smoked more and longer, drank more alcohol, had a greater dietary energy intake, were less likely to be overweight, were older and had lower educational and income levels than white controls (Table I). White ESCC cases smoked longer, drank more alcohol, were less often overweight or obese and had lower incomes than white EAC cases (Table I). White ESCC cases had higher intakes of total flavonoids, flavan-3-ols and flavonols and lower intakes of isoflavonoids than white controls and EAC cases, respectively (Table II). In addition, white ESCC cases had lower intakes of anthocyanidins from nonalcohol sources (Table II) and lower energy-adjusted (residual and nutrient density method) anthocyanidin intakes than white controls (data not shown). The mean proportions of flavonoids and proanthocyanidins from alcoholic beverages for white ESCC cases were as follows: total flavonoids (26.1%), proanthocyanidins (10.9%), anthocyanidins (46.9%), flavan-3-ols (29.1%), flavanones (2.8%), flavones (7.8%) and flavonols (37.5%). Their main dietary sources of isoflavonoids were mixed vegetables, peas other than green peas, salty snacks and mixed dishes with meat (Table III). White ESCC cases consumed less mixed vegetables and peas than white controls ($p = 0.008$ and 0.0004, respectively) and EAC cases ($p = 0.02$ and 0.06, respectively).

The only significant association was for high *vs.* low isoflavonoid consumption and ESCC risk (OR, 0.43, 95% CI, 0.20–0.93; $p_{trend} = 0.01$; Table IV; continuous OR per mg/1,000

kcal increase, 0.98, 95% CI, 0.96–1.00). Adjusting for consumption of vitamin C, raw fruits, red meats or preserved meats did not change the OR by more than 10%. No significant effect modification by smoking or drinking intensity was observed between ESCC risk and consumption of total flavonoids, proanthocyanidins or flavonoid subclasses, respectively. The only exception was that high flavone consumption was associated with decreased ESCC risk in men who smoked less than 20 cigarettes daily (p_{trend} = 0.02) but with increased ESCC risk in men who smoked at least 20 cigarettes daily (p_{trend} = 0.16; $p_{interaction}$ = 0.02).

Isoflavonoid consumption was correlated strongly with consumption of dietary fiber (0.52) and to a smaller extent with raw fruits and vegetables (0.24), raw vegetables (0.30) and cruciferous vegetables (broccoli, cooked cabbage, coleslaw, cauliflower, collards, mustard and turnip greens, kale; 0.33). After adjusting for consumption of fiber, raw fruits and vegetables, raw fruits or cruciferous vegetables, the associations between isoflavonoid consumption and ESCC in the multivariate-adjusted model were attenuated and *vice versa*. For example, the associations between isoflavonoid consumption and ESCC were OR, 0.52, 95% CI, 0.23–1.18; continuous Or, 0.99, 95% CI, 0.97–1.01 after adjusting for dietary fiber.

Flavonoid and proanthocyanidin intake and ESCC in black men

Black ESCC cases smoked more and longer, drank more alcohol, had greater energy intakes, weighed less, were slightly younger and had lower educational and income levels than black controls (Table I). Black ESCC cases consumed more total flavonoids, anthocyanidins, flavan-3-ols, flavones, flavonols (total and nonalcohol) and proanthocyanidins than did black controls (Table II). The mean proportions of flavonoids and proanthocyanidins from alcoholic beverages in black ESCC cases were as follows: total flavonoids (28.7%), proanthocyanidins (21.9%), anthocyanidins (65.2%), flavan-3-ols (31.0%), flavanones (8.6%), flavones (16.5%) and flavonols (27.3%). After energy adjustment (by both residual and nutrient density methods), black ESCC cases had higher intakes of total flavonoids, anthocyanidins, flavan-3-ols, flavones and flavonols and lower intakes of anthocyanidins (only with the nutrient density method) and flavanones from non-alcoholic sources than black controls (data not shown). The main dietary sources of flavanones (>5% of daily intake) in black controls were citrus fruit juice, oranges or tangerines and grapefruits (Table III), of which grapefruit intakes (p = 0.008) were lower in black ESCC cases than in black controls.

No significant relationships were observed in black men between ESCC risk and consumption of total flavonoids, proanthocyanidins or the flavonoid subgroups. The strongest inverse relationship was observed between ESCC risk and high vs. low flavanone intake (OR, 0.57, 95% CI, 0.30–1.08; p_{trend} = 0.08; Table IV; continuous OR per mg/1,000 kcal increase, 0.98, 95% CI, 0.97–0.999). There was no significant effect modification by smoking or drinking intensity and consumption of total flavonoids, proanthocyanidins or flavonoid subgroups.

Discussion

Our study is the first to examine the association between flavonoid and proanthocyanidin intake and EAC and ESCC in U.S. white and black men. Total flavonoid and

proanthocyanidin intake was not associated with EAC and ESCC risk in our population of heavy drinkers and smokers. However, in white men, we did observe a 53% decreased risk of EAC with greater anthocyanidin consumption and a 57% decreased risk of ESCC with greater isoflavonoid consumption. Our results are in general agreement with previous studies. An Italian hospital-based case–control study with 304 ESCC cases also did not find an association between total flavonoid intake and ESCC.[10] Similarly, a Chinese nested case–control study found no association between urinary markers of flavan-3-ol intake and esophageal cancer (42 cases of partly unspecified histology).[12] In contrast, an Uruguayan hospital-based case–control study found a decreased risk of esophageal cancer (66 cases of unspecified histology) with increased total flavonoid intake (OR, 0.4, 95% CI, 0.3–0.6).[11] In the Italian study, increased flavanone intake (*e.g.*, citrus fruits and juices) was associated with decreased risk of ESCC (OR, 0.38, 95% CI, 0.23–0.66; $p_{trend} = 0.004$),[10] which is in general agreement with the 43% decreased risk of ESCC we observed with greater flavanone consumption in black men. Associations between flavonoid consumption and EAC and the effects of isoflavonoid and proanthocyanidin consumption on any type of esophageal cancer have not been previously reported.[10–12]

Flavonoids and proanthocyanidins are potential mediators of the protective effect of raw fruit and vegetable consumption on esophageal cancer risk presumably because of their anticarcinogenic properties, including antioxidative, antimutagenic, antiinflammatory and antiproliferative effects.[7,8] The 2 flavonoid subclasses, anthocyanidins and isoflavonoids, that showed a protective effect in our study have various anticarcinogenic properties and are currently being tested in clinical trials.[20,21] Anthocyanidins and their glycosides, the anthocyanins, are of interest in EAC chemoprevention because an anthocyanin-rich berry slurry decreased markers of oxidative stress in patients with Barrett's esophagus, a premalignant lesion of EAC.[22] Isoflavonoids inhibit the growth of ESCC cell lines.[23,24] The differences in risk estimates in white men for EAC and ESCC in this and other epidemiological studies suggest that chemopreventive properties of bioactive food components might differ in their effects on EAC and ESCC.[25]

A major strength of our study is the large number of histologically classified cases, providing power to detect differences in histological subtypes and flavonoid intakes when present. The questionnaire was developed specifically for our study[13] and provided detailed information about diet and beverage consumption, including tea, coffee and various alcoholic beverages. Other strengths of the study are the variable intake of flavonoids and proanthocyanidins in this population and the ability to adjust for dietary energy intake, recognized confounding factors for esophageal cancer (including alcohol and cigarette consumption, income, education and weight) and food components that might impact risk of esophageal cancer such as fiber and vitamin C.[1]

There are limitations to our study. As with any case–control study, selection bias could impact our results as responders and nonresponders and those with acceptable and unacceptable responses to dietary questions might differ. However, controls with acceptable and unacceptable responses to dietary questions did not differ in demographic and lifestyle characteristics.[13] We cannot exclude the possibility of recall bias between cases and controls or the possibility of reverse causation because cases might have changed their diet due to

problems with gastric reflux years before diagnosis. To minimize the reverse causation, we asked about the usual adult food consumption excluding the last 5 years and did not exclude controls with a history of digestive diseases. However, participants might still have recalled a more recent food consumption pattern.[26] Our results may not be generalizable to women and populations that do not smoke, drink or do both to excess. Significant associations of flavonoid subclasses, population subgroups and histological subtypes of esophageal cancer might have arisen by chance because of multiple comparisons. However, the gradually decreasing ORs (trends) across most of the anthocyanidin and isoflavonoid intake quartiles are less likely to be due to chance.

Tea, including hot tea, is a primary source of flavonoids, especially of flavan-3-ols, flavones and flavonols, and proanthocyanidins in this cohort (Table III). Temperature and type of tea modify the association between tea consumption and esophageal cancer, especially ESCC, with hot temperatures being deleterious and green tea consumption being protective.[27] Hot tea consumption was higher in white ESCC cases than in controls (Table III; $p = 0.02$). We did not ask specifically about consumption of green tea, which has a greater flavonoid content than black tea,[16] but green tea consumption was probably low in this population. A possible protective effect of flavonoid and proanthocyanidin intake may be offset by a potentially deleterious effect of hot tea consumption.

Dietary exposure measurement error related to both the dietary assessment techniques and the flavonoid and proanthocyanidin database is likely to be present and could lead to inaccurate risk estimates. The dietary and beverage questionnaires were not specifically designed to estimate flavonoid and proanthocyanidin intake. Furthermore, limitations in the flavonoid and proanthocyanidin composition database, variations in the food quantities of recipes or grouped foods, and variability in flavonoid and proanthocyanidin content due to climatic, growing, soil and harvesting conditions of plants[28] and storage and preparation conditions of foods[6,28,29] will cause measurement error and might have led to attenuated risk estimates. These limitations especially affect risk estimates for flavones, whose intake derives mostly from garnishes and spices.[13] However, the monotonic decrease of OR in white men across anthocyanidin intake quartiles for EAC risk and across isoflavonoid intake quartiles for ESCC risk supports the contention that participants were ranked robustly enough to observe associations.

It cannot be excluded that cultural differences in storage and preparation of foods, especially of vegetables,[28,29] between black and white populations could contribute to differences in risk estimates for ESCC between black and white men, especially for isoflavonoids. Further research is warranted to quantify the flavonoid and proanthocyanidin content of foods and vegetables with different growing, storage and preparation methods to improve the accuracy of risk estimates for flavonoids and proanthocyanidins in epidemiological studies.

Alcohol and tobacco may obscure the role of flavonoids in esophageal cancer. Most ESCC and to a smaller extent EAC cases consumed large amounts of alcohol, tobacco or both, accounting for more than 90% of the risk for ESCC in this population.[30] For example, excessive alcohol consumption can alter consumption, absorption and conversion of foods and nutrients,[31] including flavonoids,[32] so that intake would not reflect the amount of

available nutrients. In addition, alcoholic beverages were a major source of flavonoids and proanthocyanidins among cases (Table II). To minimize the residual confounding by alcohol, we adjusted for types of alcoholic beverages and examined risk from nonalcohol sources. Smoking increases the exposure of the esophageal lining to carcinogenic and procarcinogenic substances, particularly when combined with ethanol which can act as a solvent or surfactant and may also decrease food consumption.[1] Although flavonoids and other bioactive food components can reduce risk of these cancers by accelerating the detoxication of carcinogenic and procarcinogenic substances,[8,33,34] they might be insufficient to overcome the stronger effects of alcohol and tobacco in this population.

Raw fruits and vegetables contain multiple chemopreventive food components, including flavonoids, isothiocyanates, fiber and vitamins.[1,35] Risk estimates are attenuated when adjusting for multiple chemopreventive food components at the same time. For example, adjusting for fiber consumption attenuated the associations between anthocyanidin and isoflavonoid consumption and EAC and ESCC, respectively. The high correlation (collinearity) between various chemopreventive food components makes it difficult to determine whether intake of anthocyanidins and isoflavonoids alone or in combination with other food components inhibits esophageal cancer.

In conclusion, total dietary flavonoids and proanthocyanidins do not have strong protective effects in this population of heavy smokers and drinkers—men at high risk for esophageal cancer. There was some suggestion that foods rich in the flavonoid subgroups anthocyanidins may be protective in EAC and isoflavonoids in ESCC. These results are intriguing and warrant further research in the potential chemopreventive role of flavonoids, especially anthocyanidins in EAC and isoflavonoids in ESCC. Improved flavonoid and proanthocyanidin databases and confirmation of our results in prospective studies, which include women, are needed before definite conclusions can be made about the role of dietary flavonoids and proanthocyanidins in the etiology of EAC and ESCC.

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TABLE I -

CHARACTERISTICS OF WHITE AND BLACK MEN WITH OR WITHOUT ESOPHAGEAL ADENOCARCINOMA (EAC) AND SQUAMOUS CELL CANCER (ESCC) LIVING IN 3 AREAS OF THE UNITED STATES (1986–1989)

Characteristic	White-Control (*N* = 678)	White-EAC (*N* = 161)	White-ESCC (*N* = 114)	Black-Control (*N* = 557)	Black-ESCC (*N* = 218)
	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)
Age (years)					
<50	116 (17.1)	17 (10.6)	8 (7.0)	78 (14.0)	33 (15.1)
50–59	198 (29.2)	38 (23.6)	31 (27.2)	132 (23.7)	70 (32.1)
60–69	200 (29.5)	65 (40.4)	51 (44.7)	172 (30.9)	90 (41.3)
≥70	164 (24.2)	41 (25.5)	24 (21.1)	175 (31.4)	25 (11.5)
Area					
Atlanta	159 (23.5)	19 (11.8)	7 (6.1)	122 (21.9)	40 (18.4)
Detroit	246 (36.3)	112 (69.6)	51 (44.7)	233 (41.8)	84 (38.5)
New Jersey	273 (40.3)	30 (18.6)	56 (49.1)	202 (36.3)	94 (43.1)
Education (years)					
No answer	2 (0.3)	0 (.0)	0 (.0)	0 (.0)	1 (0.5)
<High school	169 (24.9)	56 (34.8)	48 (42.1)	329 (59.1)	159 (72.9)
High school	170 (25.1)	37 (23.0)	29 (25.4)	107 (19.2)	45 (20.6)
>High school	337 (49.7)	68 (42.2)	37 (32.5)	121 (21.7)	13 (6.0)
Smoking duration (years)					
None	213 (31.4)	25 (15.5)	16 (14.0)	169 (30.3)	20 (9.2)
<30	205 (30.2)	55 (34.2)	16 (14.0)	131 (23.5)	34 (15.6)
30–39	113 (16.7)	37 (23.0)	24 (21.1)	86 (15.4)	46 (21.1)
≥40	147 (21.7)	44 (27.3)	58 (50.9)	171 (30.7)	118 (54.1)
Smoking intensity (cigarettes/day)					
None	213 (31.4)	25 (15.5)	16 (14.0)	169 (30.3)	20 (9.2)
<20	108 (15.9)	17 (10.6)	13 (11.4)	171 (30.7)	54 (24.8)
20–39	246 (36.3)	85 (52.8)	52 (45.6)	182 (32.7)	113 (51.8)
≥40	111 (16.4)	34 (21.1)	33 (29.0)	35 (6.3)	31 (14.2)
Alcohol consumption (drinks/day)					
None	149 (22.0)	29 (18.0)	2 (1.8)	130 (23.3)	3 (4.1)

Characteristic	White-Control (*N* = 678)	White-EAC (*N* = 161)	White-ESCC (*N* = 114)	Black-Control (*N* = 557)	Black-ESCC (*N* = 218)
	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)
≤1	196 (28.9)	34 (21.1)	10 (8.8)	118 (21.2)	9 (4.2)
1–2	120 (17.7)	25 (15.7)	12 (10.5)	94 (16.9)	22 (10.1)
2–5	135 (19.9)	38 (23.6)	30 (26.3)	132 (23.7)	63 (28.9)
5–12	57 (8.8)	25 (15.5)	43 (37.7)	60 (11.3)	77 (37.2)
≥12	18 (2.7)	8 (5.0)	17 (14.9)	20 (3.6)	40 (18.3)
Energy intake (quartiles in kcal/day)					
1 (<1,370)	155 (22.9)	25 (15.5)	18 (15.8)	154 (27.7)	45 (20.6)
2 (1,370–1,769)	177 (26.1)	41 (25.5)	25 (21.9)	132 (23.7)	47 (21.6)
3 (1,770–2,180)	186 (27.4)	38 (23.6)	34 (29.8)	123 (22.1)	48 (22.0)
4 (>2,180)	160 (23.6)	57 (35.4)	37 (32.5)	148 (26.6)	78 (35.8)
Body mass index (kg/m^2)					
<25	322 (47.5)	52 (32.3)	63 (55.3)	263 (47.2)	157 (72.0)
25–29.9	311 (45.9)	78 (48.5)	36 (31.6)	241 (43.3)	51 (23.4)
≥30	45 (6.6)	31 (19.3)	15 (13.2)	53 (9.5)	10 (4.6)
Income ($/year)					
No answer	44 (6.5)	15 (9.3)	3 (2.6)	36 (6.5)	11 (5.1)
<10,000	48 (7.1)	22 (13.7)	28 (24.6)	150 (26.9)	127 (58.3)
10,000–24,999	215 (31.7)	58 (36.0)	50 (43.9)	217 (39.0)	60 (27.5)
25,000–49,999	203 (29.9)	44 (27.3)	22 (19.3)	111 (19.9)	19 (8.7)
≥50,000	168 (24.8)	22 (13.7)	11 (9.7)	43 (7.7)	1 (0.5)

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TABLE II -

MEDIANS AND INTERQUARTILE RANGES OF DAILY INTAKES OF TOTAL FLAVONOIDS, FLAVONOID SUBCLASSES AND PROANTHOCYANIDINS AMONG WHITE AND BLACK MEN WITH OR WITHOUT ESOPHAGEAL ADENOCARCINOMA (EAC) AND SQUAMOUS CELL CANCER (ESCC)

Dietary component	White-Control (*N* = 678)	White-EAC (*N* = 161)	White-ESCC (*N* = 114)	Black-control (*N* = 557)	Black-ESCC (*N* = 218)
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Flavonoids (in mg/day)					
Total flavonoids	122 (72.9–194)	129 (69.8–229)	176 (91.2–273)**	114 (60.3–174)	135 (70.3–231)**
Anthocyanidins	4.61 (2.51–8.83)	4.46 (1.69–8.19)	3.78 (2.10–8.44)	6.12 (3.04–10.6)	6.84 (3.47–16.4)**
Flavan-3-ols	55.7 (16.9–109)	53.1 (22.6–136)	101 (34.9–170)**	33.3 (10.2–90.7)	54.3 (17.8–114)**
Flavanones	26.8 (15.4–45.4)	28.2 (17.1–47.6)	24.7 (11.1–49.1)	27.5 (14.5–50.8)	24.3 (13.3–46.5)
Flavones	5.43 (3.64–7.71)	5.30 (3.49–7.75)	5.91 (3.46–8.46)	6.53 (4.21–9.39)	7.28 (4.92–11.1)**
Flavonols	19.5 (12.1–28.5)	21.0 (12.9–33.4†	28.6 (17.6–39.9)**	20.7 (12.8–31.1)	26.2 (16.7–39.1)**
Isoflavonoids	0.021 (0.008–0.033)	0.020 (0.009–0.033)	0.014 (0.005–0.025)**	0.022 (0.011–0.037)	0.021 (0.011–0.035)
Proanthocyanidins	241 (77.4–496)	230 (70.7–534)	324 (74.9–632)	154 (49.2–414)	219 (52.8–505)*
Flavonoids nonalcohol (in mg/day)					
Total flavonoids	102 (56.5–175)	99.4 (53.9–181)	129 (47.6–203)	97.5 (52.3–160)	95.6 (47.3–169)
Anthocyanidins	4.34 (2.37–7.52)	3.77 (1.59–6.75†	3.26 (1.77–6.36)**	5.53 (2.89–9.63)	5.10 (2.71–8.29)
Flavan-3-ols	44.9 (8.49–97.4)	36.5 (8.41–106)	53.7 (6.20–130)	18.3 (5.30–86.7)	17.4 (3.63–91.7)
Flavanones	26.3 (14.9–44.6)	28.0 (16.6–46.7)	24.7 (3.46–8.46)	26.5 (13.7–49.2)	23.5 (11.8–41.5)
Flavones	5.19 (3.49–7.54)	5.17 (3.38–7.41)	5.45 (2.70–8.35)	6.36 (4.11–9.08)	6.56 (4.53–10.1)
Flavonols	14.7 (9.54–24.5)	15.5 (9.08–24.7)	16.8 (9.00–27.0)	17.2 (10.9–27.7)	18.7 (12.9–29.7)*
Isoflavonoids	0.021 (0.008–0.033)	0.020 (0.009–0.033)	0.014 (0.005–0.025)**	0.022 (0.011–0.037)	0.021 (0.011–0.035)
Proanthocyanidins	230 (60.7–485)	202 (53.3–476)	271 (43.1–595)	143 (42.5–404)	120 (29.1–437)

† $p < 0.10$;

* $p < 0.05$;

** $p < 0.01$ based on Wilcoxon rank–sum test; comparisons between white EAC versus white control, white ESCC versus white control and black ESCC versus black control.

TABLE III -

MAIN DIETARY SOURCES OF TOTAL FLAVONOIDS, FLAVONOID SUBCLASSES AND PROANTHOCYANIDINS (AT LEAST 5% OF DAILY INTAKE, IN mg/day) AMONG WHITE AND BLACK MEN WITH OR WITHOUT ESOPHAGEAL ADENOCARCINOMA (EAC) AND SQUAMOUS CELL CANCER (ESCC)

Flavonoid	Food/food group	White-control (*N* = 678)	White-EAC (*N* = 161)	White-ESCC (*N* = 114)	Black-control (*N* = 557)	Black-ESCC (*N* = 218)
		Intake (%)	Intake (%)	Intake (%)	Intake (%)	Intake (%)
Total flavonoids	Iced tea	48.4 (32.4)	48.1 (30.5)	49.2 (24.3)	33.8 (24.2)	40.2 (22.2)
	Hot tea	25.7 (17.2)	24.6 (15.6)	46.3 (22.9)	18.4 (13.2)	24.6 (13.6)
	Citrus fruit juice	14.0 (9.35)	12.9 (8.18)	12.5 (6.17)	14.6 (10.4)	14.7 (8.11)
	Beer	12.5 (8.34)	18.2 (11.6)	42.2 (20.9)	11.0 (7.85)	19.2 (10.6)
	Oranges	10.6 (7.07)	11.7 (7.43)	10.1 (5.00)	12.8 (9.12)	12.3 (6.79)
	Grapefruits	8.80 (5.89)	10.5 (6.65)	10.5 (5.21)	9.68 (6.91)	5.40 (2.97)
	Red wine	5.11 (3.42)	6.36 (4.04)	10.3 (5.10)	7.12 (5.08)	31.3 (17.3)
	Collards/kale	1.25 (0.84)	1.05 (0.67)	0.17 (0.09)	8.04 (5.74)	8.65 (4.76)
Anthocyanidins	Bananas	2.44 (33.5)	2.08 (28.6)	2.31 (28.6)	2.36 (24.9)	1.74 (9.56)
	Red wine	1.88 (25.8)	2.33 (32.0)	3.78 (46.8)	2.61 (27.5)	11.5 (63.2)
	Apples/pears	1.48 (20.3)	1.53 (20.9)	1.04 (12.9)	1.59 (16.7)	1.21 (6.66)
	Peas non green	0.72 (9.88)	0.46 (6.32)	0.24 (2.91)	2.30 (24.2)	2.80 (15.4)
Flavan-3-ols	Iced tea	39.2 (49.1)	39.0 (46.6)	39.9 (32.9)	27.4 (44.9)	32.6 (37.8)
	Hot tea	22.2 (27.8)	21.3 (25.5)	40.1 (33.0)	16.0 (26.1)	21.3 (24.7)
	Beer	9.25 (11.6)	13.5 (16.1)	31.3 (25.8)	8.16 (13.3)	14.2 (16.5)
	Apples/pears	2.88 (3.61)	2.97 (3.55)	2.03 (1.67)	3.09 (5.05)	2.36 (2.73)
	Red wine	1.92 (2.41)	2.39 (2.86)	3.88 (3.20)	2.68 (4.38)	11.8 (13.7)
Flavanones	Citrus fruit juice	12.1 (35.9)	11.2 (31.5)	10.8 (31.8)	12.6 (34.0)	12.7 (36.3)
	Oranges	10.1 (30.1)	11.2 (31.3)	9.70 (28.5)	12.3 (33.0)	11.8 (33.7)
	Grapefruits	8.64 (25.7)	10.3 (28.9)	10.3 (30.4)	9.50 (25.6)	5.30 (15.1)
	Iced tea	1.80 (5.36)	1.79 (5.03)	1.83 (5.40)	1.26 (3.39)	1.50 (4.27)
	Red wine	0.44 (1.31)	0.55 (1.54)	0.89 (2.62)	0.61 (1.65)	2.70 (7.70)
Flavones	Citrus fruit juice	1.61 (26.5)	1.49 (23.8)	1.44 (22.6)	1.69 (22.3)	1.70 (18.2)
	Iced tea	1.37 (22.6)	1.36 (21.8)	1.40 (21.9)	0.96 (12.7)	1.14 (12.2)
	Vegetable soup	0.63 (10.4)	0.75 (12.0)	0.69 (10.8)	0.58 (7.68)	0.66 (7.10)

Flavonoid	Food/food group	White-control (*N* = 678)	White-EAC (*N* = 161)	White-ESCC (*N* = 114)	Black-control (*N* = 557)	Black-ESCC (*N* = 218)
		Intake (%)	Intake (%)	Intake (%)	Intake (%)	Intake (%)
	Hot tea	0.47 (7.74)	0.45 (7.22)	0.85 (13.3)	0.34 (4.47)	0.45 (4.83)
	Oranges	0.43 (7.07)	0.48 (7.64)	0.41 (6.47)	0.52 (6.88)	0.50 (5.37)
	Collards/kale	0.34 (5.53)	0.28 (4.53)	0.05 (0.73)	2.16 (28.6)	2.33 (24.9)
	Red wine	0.24 (4.02)	0.30 (4.87)	0.49 (7.74)	0.34 (4.50)	1.50 (16.0)
Flavonols	Iced tea	5.98 (26.5)	5.94 (24.0)	6.08 (18.8)	4.18 (17.0)	4.97 (15.2)
	Beer	3.21 (14.2)	4.68 (18.9)	10.9 (33.6)	2.83 (11.5)	4.94 (15.1)
	Hot tea	2.99 (13.3)	2.87 (11.6)	5.39 (16.7)	2.15 (8.71)	2.87 (8.79)
	Apples/pears	1.49 (6.61)	1.54 (6.22)	1.05 (3.24)	1.60 (6.49)	1.22 (3.74)
	Vegetable stew	1.19 (5.25)	1.36 (5.49)	1.49 (4.59)	1.53 (6.20)	1.75 (5.39)
	Collards/kale	0.91 (4.05)	0.77 (3.11)	0.13 (0.39)	5.87 (23.8)	6.32 (19.4)
	Coffee	0.91 (4.04)	1.26 (5.09)	1.00 (3.10)	0.44 (1.77)	0.50 (1.54)
	Red wine	0.63 (2.77)	0.78 (3.15)	1.26 (3.90)	0.87 (3.54)	3.82 (11.7)
Isoflavonoid	Mixed vegetables	0.019 (73.1)	0.019 (74.6)	0.015 (72.8)	0.017 (59.3)	0.014 (50.2)
	Peas non-green	0.002 (9.53)	0.002 (6.16)	0.001 (4.03)	0.008 (28.3)	0.010 (35.7)
	Salty snacks	0.002 (9.00)	0.003 (10.3)	0.003 (12.5)	0.002 (6.00)	0.002 (6.84)
	Meat dishes	0.001 (5.19)	0.002 (5.98)	0.001 (7.08)	0.001 (3.73)	0.001 (4.70)
Proanthocyanidins	Iced tea	200 (55.8)	199 (54.9)	203 (45.7)	140 (50.3)	166 (44.1)
	Hot tea	80.5 (22.5)	77.1 (21.3)	145 (32.6)	57.7 (20.7)	77.2 (20.5)
	Apples/pears	37.2 (10.4)	38.4 (10.6)	26.2 (5.88)	39.9 (14.3)	30.5 (8.09)
	Red wine	11.3 (3.16)	11.1 (3.06)	22.8 (5.12)	15.8 (5.66)	11.7 (3.09)
	Beer	7.58 (2.11)	14.1 (3.90)	25.7 (5.76)	6.68 (2.40)	69.4 (18.4)

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TABLE IV -

ASSOCIATIONS BETWEEN TOTAL FLAVONOID, FLAVONOID SUBCLASS AND PROANTHOCYANIDIN CONSUMPTION AND ESOPHAGEAL ADENOCARCINOMA (EAC) AND SQUAMOUS CELL CANCER (ESCC) AMONG WHITE AND BLACK MEN

Flavonoid[1]	Intake	White cases/control *n/n* 161/678	White-EAC OR (95% CI) *N* = 161	White cases/control *n/n* 114/678	White-ESCC OR (95% CI) *N* = 114	Intake	Black cases/control *n/n* 218/557	Black-ESCC OR (95% CI) *N* = 218
Flavonoids (in mg/1,000 kcal)								
Total flavonoids	Low <43.0	45/170	Ref.	19/170	Ref.	Low <38.6	45/140	Ref.
	43.0–69.4	36/169	0.80 (0.44-.43)	26/169	0.91 (0.41–1.99)	38.6–61.7	51/139	0.82 (0.43–1.56)
	69.5–107	42/170	0.97 (0.53–1.76)	19/170	0.54 (0.23–1.28)	61.8–99.6	46/139	0.59 (0.30–1.16)
	High >107	38/169	0.71 (0.36–1.42)	50/169	1.19 (0.50–2.81)	High >99.6	76/139	0.72 (0.35–1.46)
	p_{trend}		0.42		0.50			0.40
Anthocyanidins	Low <1.45	55/170	Ref.	35/170	Ref.	Low <1.88	49/140	Ref.
	1.45–2.66	38/169	0.60 (0.35–1.02)	34/169	0.81 (0.42–1.56)	1.88–3.31	52/139	1.26 (0.69–2.31)
	2.67–4.72	40/170	0.63 (0.36–1.07)	19/170	0.75 (0.35–1.59)	3.31–5.77	44/139	1.18 (0.64–2.20)
	High >4.73	28/169	0.47 (0.24–0.91)	26/169	0.73 (0.32–1.67)	High >5.77	73/139	0.86 (0.42–1.75)
	p_{trend}		0.04		0.48			0.56
Flavan-3-ols	Low <10.3	35/170	Ref.	14/170	Ref.	Low <6.17	39/140	Ref.
	10.3–31.2	39/169	1.19 (0.64–2.23)	31/169	0.85 (0.36–2.02)	6.17–18.5	41/139	0.86 (0.41–1.78)
	31.3–60.6	46/170	1.58 (0.82–3.05)	20/170	0.54 (0.20–1.42)	18.6–49.4	70/139	0.92 (0.45–1.87)
	High >60.6	41/169	1.22 (0.60–2.49)	49/169	0.95 (0.36–2.52)	High >49.4	68/139	0.78 (0.36–1.68)
	p_{trend}		0.69		0.82			0.56
Flavanones	Low <9.30	42/170	Ref.	38/170	Ref.	Low <8.85	62/140	Ref.
	9.30–15.6	40/169	0.90 (0.52–1.56)	22/169	0.82 (0.41–1.65)	8.85–15.9	56/139	0.89 (0.49–1.62)
	15.7–26.2	38/170	0.94 (0.53–1.65)	29/170	1.07 (0.54–2.12)	16.0–26.3	58/139	0.92 (0.50–1.69)
	High >26.2	41/169	0.99 (0.56–1.75)	25/169	0.94 (0.47–1.90)	High >26.3	42/139	0.57 (0.30–1.08)
	p_{trend}		0.94		0.98			0.08
Flavones	Low <2.08	45/170	Ref.	34/170	Ref.	Low <2.52	43/140	Ref.
	2.08–3.15	46/169	0.92 (0.54–1.57)	31/169	0.94 (0.49–1.81)	2.52–3.73	49/139	1.28 (0.69–2.39)
	3.16–4.41	36/170	0.93 (0.52–1.66)	23/170	0.79 (0.38–1.64)	3.74–5.27	54/139	1.10 (0.59–2.06)
	High >4.41	34/169	0.81 (0.43–1.51)	26/169	0.79 (0.36–1.73)	High >5.27	72/139	1.02 (0.52–2.00)

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Flavonoid[1]	Intake	White cases/control *n/n* 161/678	White-EAC OR (95% CI) *N* = 161	White cases/control *n/n* 114/678	White-ESCC OR (95% CI) *N* = 114	Intake	Black cases/control *n/n* 218/557	Black-ESCC OR (95% CI) *N* = 218
	p_{trend}		0.53		0.50			0.87
Flavonols	Low <6.89	35/170	Ref.	15/170	Ref.	Low <8.05	36/140	Ref.
	6.89–11.0	42/169	1.19 (0.66–2.17)	17/169	0.66 (0.27–1.62)	8.06–11.8	42/139	1.58 (0.80–3.10)
	11.1–15.9	40/170	1.26 (0.67–2.38)	31/170	0.93 (0.38–2.25)	11.9–17.1	54/139	1.07 (0.54–2.11)
	High >15.9	44/169	0.98 (0.47–2.01)	51/169	1.09 (0.41–2.87)	High >17.1	86/139	1.11 (0.54–2.30)
	p_{trend}		0.79		0.50			0.86
Isoflavonoids	Low <.005	40/170	Ref.	42/170	Ref.	Low <.007	61/140	Ref.
	0.005–0.010	47/169	0.74 (0.43–1.29)	36/169	0.81 (0.43–1.50)	0.007–0.012	67/139	1.09 (0.61–1.96)
	0.011–0.019	42/170	0.65 (0.37–1.15)	20/170	0.44 (0.21–0.91)	0.013–0.020	41/139	0.55 (0.29–1.03)
	High >.019	32/169	0.65 (0.36–1.18)	16/169	0.43 (0.20–0.93)	High >0.020	49/139	0.91 (0.50–1.64)
	p_{trend}		0.20		0.01			0.55
Proanthocyanidins	Low <45.5	44/170	Ref.	29/170	Ref.	Low <32.7	63/140	Ref.
	45.5–135	39/169	0.93 (0.52–1.64)	22/169	0.59 (0.28–1.27)	32.8–84.2	30/139	0.43 (0.22–0.84)
	136–272	41/170	1.18 (0.63–2.22)	24/170	0.62 (0.27–1.43)	84.3–216	55/139	0.49 (0.25–0.93)
	High >272	37/169	0.89 (0.46–1.70)	39/169	1.02 (0.46–2.26)	High >216	70/139	0.58 (0.30–1.13)
	p_{trend}		0.76		0.49			0.54

[1]Adjusted for smoking duration and intensity, geographical area, age, body mass index, hot tea consumption, hard liquor consumption, beer consumption, “moonshine” consumption (only for black men), red wine consumption, white wine consumption (except for ESCC in white men), caloric intake, education (only for black men) and income.