The risk of lung cancer related to dietary intake of flavonoids

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ABSTRACT

It has been hypothesized that flavonoids in foods and beverages may reduce cancer risk through antioxidation, inhibition of inflammation, and other antimutagenic and antiproliferative properties. We examined associations between intake of five flavonoid subclasses (anthocyanidins, flavan-3-ols, flavones, flavonols, flavanones) and lung cancer risk in a population-based case-control study in Montreal, Canada (1,061 cases and 1,425 controls). Flavonoid intake was estimated from a food frequency questionnaire that assessed diet two years prior to diagnosis (cases) or interview (controls). Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression. Overall, total flavonoid intake was not associated with lung cancer risk, the effect being similar regardless of sex and smoking level. However, low flavonoid intake from food, but not from beverages, was associated with an increased risk. The adjusted ORs (95% CIs) comparing the highest versus the lowest quartiles of intake were 0.63 (0.47-0.85) for total flavonoids, 0.82 (0.61-1.11) for anthocyanidins, 0.67 (0.50-0.90) for flavan-3-ols, 0.68 (0.50-0.93) for flavones, 0.62 (0.45-0.84) for flavonols, and 0.70 (0.53-0.94) for flavanones. An inverse association with total flavone and flavanone intake was observed for squamous cell carcinoma but not adenocarcinoma. In conclusion, low flavonoid intake from food may increase lung cancer risk.

Keyword: lung cancer, diet, flavonoids, case-control study, epidemiological

INTRODUCTION

Between 80-90% of lung cancers are attributable to smoking in North American populations (1), however, it is clear that other factors influence risk as lung cancer also occurs among individuals who have never smoked (2). Furthermore, not all smokers (about 15%) eventually develop lung cancer (3), suggesting that other factors may modify the risk associated with tobacco carcinogens. Flavonoids are a family of polyphenols abundant in fruits, vegetables, and some beverages including tea, beer, and wine. There are about 8,000 individual flavonoid compounds in foods, which are categorized in six major subclasses: flavonols, flavones, flavanones, flavan-3-ols (also referred to as catechins), anthocyanidins, and isoflavones (4). Flavonoids have multiple biological properties that may contribute to the lower lung cancer risk often associated with fruits and vegetables, including antioxidant activity, inflammation inhibition, as well as other antimutagenic and antiproliferative properties (5, 6). Although findings have been somewhat inconsistent, there is evidence from animal studies that dietary flavonoids can be found in lung tissue and thus may exert a role in cancer prevention (7-9).

Among previous studies that have examined flavonoid intake in relation to lung cancer, several have reported statistically significant risk reductions of 17-76% for the highest versus lowest intakes of the flavonol, flavone and flavan-3-ol subclasses (10-17). However, other studies have reported no association (18-24), or a risk reduction only among smokers (10, 21). These differences may be due to differing sources (i.e. food or beverage) and types of flavonoids measured, or different distributions of other lung cancer determinants (i.e. smoking). Another possible reason for inconsistencies is that until recently, existing food composition databases included only a limited number of flavonoid compounds and flavonoid- containing foods (25,

26). Thus, although many past studies examined flavonols and flavones, few have examined flavan-3-ols (10, 16, 19-21, 23), flavanones (10, 14-16, 21-23), and anthocyanidins (16). In 2003 the US Department of Agriculture (USDA) produced a comprehensive food composition database for flavonoids that includes over 250 foods and 19 different flavonoid compounds among five subclasses (27). The USDA database, updated in 2007 (28), uses high quality control.

In the context of a population-based case-control study of lung cancer carried out in Montreal, Canada, information was collected on a number of personal, lifestyle and environmental factors, including diet. We used these data to examine the association between flavonoid intake and lung cancer risk among men and women.

MATERIALS AND METHODS

Study population

This study, described in detail elsewhere (29), included male and female Canadians aged 35 to 75 years old who resided in the greater Montreal area. Newly diagnosed lung cancer cases occurring between January 1996 and December 1997 were identified at 18 hospitals, capturing over 98% of diagnoses in the study base. Overall, 1,429 men and women with histologically confirmed incident lung cancer were eligible and 84% (n=738 men, 465 women) participated. Interviews were conducted an average of 12.1 months after diagnosis. If a participant had died before the interview or was too ill, the interview was conducted with the next of kin. Histological type was confirmed by pathology reports (30). The sampling frame used to select population controls was the Provincial Electoral List. Population controls were randomly selected, stratified

to the expected age (± 5 years) and sex distribution of cases. Among 2,179 potential controls that were approached, 69% (n=899 men, 614 women) participated. After excluding persons with incomplete food frequency questionnaire (FFQ) information (>50% of FFQ items missing; n=162), extreme energy intakes (i.e. >3 standard deviations [SD] from the log-transformed mean total energy intake; n=27), extreme alcohol intakes (upper 1% [i.e. reporting >24 drinks daily]; n=8) and missing smoking data (n=33), 2486 persons remained (1,061 cases and 1,425 controls). Written informed consent was obtained from participants, and the study was approved by the Institutional Review Boards of all the participating Universities and hospitals.

Data collection and assessment of flavonoids

In-person interviews were conducted to assess socio-demographic and lifestyle characteristics (including smoking, diet and beverage intake) and detailed occupational history (31). Diet from two years prior to diagnosis (cases) or interview (controls) was assessed using a semiquantitative FFQ developed by the Canadian Cancer Registries Epidemiology Research Group (32), with modifications to reflect the diet of our study population, to capture major sources of carotenoids and vitamin C, and to abbreviate questionnaire length. The FFQ included 42 items, including 77 fruits, vegetables, meats, dairy products and grain products. Participants reported their usual frequency of consumption of a typical portion in categories of: 7+ times/week, 4-6 times/week, 1-3 times/week, 1-3 times/month, or never or <1 time/month. Participants also reported whether they consumed coffee, tea and alcohol (i.e. wine, beer and spirits) regularly, and if so, their average daily consumption. Consistent with the FFQ data, beverage consumption 2 years prior to interview was used. Portion sizes were converted into grams using Health Canada's Canadian Nutrient File (33). Daily intake of each food in grams per day (g/day) was calculated by

multiplying participants' reported frequency of intake of the typical portion (in days) by the number of grams in that portion.

Intake indices were computed for the following five flavonoid subclasses (with example high contributors from our specific FFQ): anthocyanidins (berries, red wine), flavan-3-ols (tea, red wine), flavones (red wine, citrus fruit), flavonols (apples, pears, tea), and flavanones (citrus fruit). Isoflavone intake was not analyzed because tofu, other soy products and other isoflavone-rich foods, such as chickpeas and peanuts (34) were not on the FFQ. Flavonoid content in foods and beverages was determined using the most recent 2007 USDA database (28). For each food/beverage, the specific flavonoid compound value in milligrams per 100 grams of food/beverage was extracted from the USDA database. For grouped food items, a weighted average of flavonoid content was calculated (35), where weights were based on average per capita consumption of each food (36). Red versus white wine consumption was weighted according to recent consumption statistics (37) and tea intake was assumed to be only black tea based on local habits before the 1990s. Since flavonoid content can vary according to the form of the food (e.g. fresh, canned or frozen), we further weighted flavonoid values according to the relative consumption of the different forms (36). Since cooking can change flavonoid content, we used data from an FFQ validation study in Montreal conducted during the same time period (38) to weight flavonoid content values for some vegetables (asparagus, broccoli, carrots, cabbage, cauliflower, Brussels sprouts, spinach, peas, corn and tomatoes) according to raw versus cooked.

Daily consumption of each flavonoid subclass was calculated by multiplying the flavonoid content for each food/beverage by the frequency of intake (in grams per day) of that item. Total flavonoid intake was calculated as the summed total of each of the flavonoid subclasses. Flavonoid intake was adjusted for total energy using the residual method (39).

Statistical analysis

Total flavonoid intake and total intake of each of the five flavonoid subclasses were analyzed in separate multivariable models. Unconditional logistic regression was used to estimate odds ratios (ORs) and associated 95% confidence intervals (CIs). Flavonoid intake was analyzed as categorical variables, where intake was divided into sex-specific quartiles based on the distribution among controls.

In multivariable models, associations were adjusted for age at diagnosis/interview (continuous), sex, respondent status (self, proxy), ethnic origin (French Canadian, other), education (<7 years, 7-12 years, ≥12 years), mean census tract family income (low, medium, high), alcohol intake (continuous, drinks/day), body mass index (BMI, kg/m^2; underweight [<18.5], normal [18.5-24.9], overweight [25-29.9], obese [≥30]), total energy intake (continuous, kilocalories/day), occupational exposure to major lung carcinogens (ever exposure to asbestos, arsenic/arsenic compounds, beryllium, silica, cadmium, chromium, and/or nickel compounds), and cigarette smoking. These variables were selected *a priori*, based only on the following criteria: they were known to be associated with lung cancer and they were available in our database. Further, these variables were associated with flavonoid intake in this study population (data not shown), and are unlikely to lie on the causal pathway between exposure (flavonoid intake) and outcome (lung

cancer). Cigarette smoking was modeled using the comprehensive smoking index (CSI), which is a continuous variable that aggregates information on smoking status (ever, never), duration and smoking intensity (pack-years), and for former smokers, the number of years since quitting smoking, in a single measure (40). This index has been successfully used to parameterize smoking history in this population (40).

Modification of the ORs by sex and smoking was evaluated by including product terms for the flavonoid variable and the effect modifier of interest. The p-value for multiplicative interaction was based on the likelihood ratio test comparing models with and without the product terms. Smoking level was dichotomized as light-smokers and moderate/heavy-smokers based on the distribution of the CSI among ever smokers. Never-smokers (n=47 cases, n=445 controls) were combined with light-smokers, defined as persons in the lowest quartile of the CSI among ever smokers. We acknowledge that this category includes some participants with a nontrivial risk of lung cancer due to smoking; the OR (95% CI) comparing light to never smokers was 2.00 (1.37-2.93). However, the number of cases that never smoked is too small to support separate analyses. The OR (95% CI) comparing the moderate/heavy smokers with the combined never/light smoker group is 10.41 (8.44-12.84), showing that these are meaningfully different groups with respect to smoking, and therefore informative to assess effect modification.

Because beverage intake was assessed on a questionnaire separate from the FFQ and since polyphenols may be absorbed differently from different foods and beverages (41), we performed separate analyses for flavonoids from food versus beverage sources (i.e. tea, wine, beer).

We also examined associations by lung cancer histology (adenocarcinoma, squamous cell carcinoma, and small cell carcinoma) using polytomous logistic regression. To test if the associations between quartiles of flavonoid intake and lung cancer risk differed by histology, we fit one model, where for each quartile of the flavonoid distribution, we estimated separate regression coefficients for each of the three histologic types, and then a second model using the same data, where we forced the three corresponding regression coefficients for a given quartile to have the same value regardless of the histologic subtype. We then used a 6-degree-of-freedom likelihood ratio test of homogeneity to test if the first model fit the polytomous data significantly better than the second, restricted model. All statistical tests were two-sided and a p-value of less than 0.05 was considered to be statistically significant. All analyses were performed using STATA version 8.

RESULTS

The study population is described in table 1. For men, the mean age was 64.2 years (SD=7.8) for cases and 64.9 (SD=7.6) for controls; for women the mean age was 61.4 (SD=9.4) for cases and 61.4 (SD=9.3) for controls. Approximately 1/3 of interviews among cases were completed by proxy, usually the spouse, compared with fewer than 10% among controls. A higher proportion of cases reported French ancestry, and cases were more likely to have lower family income and fewer years of schooling. As expected, a higher proportion of cases were former or current smokers. The majority of lung cancers were adenocarcinoma or squamous cell carcinoma.

The median (interquartile range) of total flavonoid intake, calculated by summing intake of all five subclasses was 108.8 (53.7- 434.2) mg/day for cases and 117.7 (69.6-340.6) mg/day for

controls. Intake of flavonoid subclasses was similar to previous studies that used the USDA flavonoids database (10, 16, 21, 23). Table 2 shows the food and beverage items that contributed most to each of the flavonoid subclasses in our study population. Intake of black tea was the largest contributor to total flavonoid intake.

Pairwise linear Pearson correlation coefficients (r) between total intake of each of the flavonoid subclasses ranged from the absence of any correlation (r=-0.08) between flavones and flavan-3-ols to near-collinearity (r=0.94) between flavonols and flavan-3-ols. There was moderately high correlation between vitamin C and total flavone (r=0.45) and flavanone (r=0.54) intake, as well as between the carotenoid beta-cryptoxanthin and these same flavonoid classes (r=0.47 and 0.51).

Table 3 shows both crude and adjusted ORs of lung cancer for each quartile of intake, relative to the lowest quartile, for each of the five flavonoid subclasses and for all flavonoids combined. While most of the crude ORs were statistically significantly below 1.00, in multivariable models the ORs were attenuated and a statistically significant inverse association for the highest versus lowest intake was observed only for flavones and flavanones. For anthocyandins and flavonols, a statistically significant relative risk below 1.00 was observed in the third versus the first quartile, while for total flavonoids a statistically significant inverse association was observed in the second quartile. Smoking was the covariate whose inclusion in the model resulted in the greatest attenuation of the ORs for all flavonoid variables (>10% change in OR). When analyses were conducted using the standard multivariable approach to adjust for total energy intake, rather than the residual method, results were similar (not shown).

For each of the flavonoid subclasses, there was no evidence of statistically significant effect modification by sex (table 4), except for anthocyandins, where an inverse association was more apparent among females. Similarly, there was no statistically significant effect modification by smoking level (table 4), though the ORs in the third quartile of intake of total flavonoids, flavan-3-ols, and flavonols suggested increased risks among never-light smokers and reduced risks among moderate-heavy smokers.

When considering flavonoids from beverage sources only there was no evidence of an association for any of the six flavonoid variables. In contrast, for flavonoids from food sources, statistically significant inverse associations were observed for all flavonoids except for anthocyanidins (table 5). Because of the high contribution of tea to some flavonoid groups, in a sensitivity analysis, we calculated intake of each flavonoid without the contribution of tea and observed results similar to the results that considered food sources only, with the ORs decreasing monotonically with increasing quartiles of flavonoid intake. The adjusted ORs (95% CI) systematically indicated risk reductions for the highest versus lowest quartiles of flavonoid intake from non-tea sources, and were 0.63 (0.46-0.84) for total flavonoids, 0.86 (0.64-1.15) for anthocyanidins, 0.57 (0.42-0.77) for flavan-3-ols, 0.68 (0.51-0.92) for flavones, 0.54 (0.40-0.73) for flavonols, and 0.71 (0.53-0.95) for flavanones).

For most of the flavonoid variables, the pattern of ORs across the four quartiles of total intake did not vary significantly across the different histological types (table 6), except for flavones and flavanones. For flavones, the risk of squamous cell carcinoma was significantly reduced for all three higher quartiles of intake relative to the lowest intake, while associations were closer to the

null for small cell carcinoma and adenocarcinoma. Similarly, flavanone intake was inversely associated with squamous cell carcinoma, but not with adenocarcinoma or small cell carcinoma. However, for flavanones, the heterogeneity of the associations were statistically non-significant when applying the Bonferroni-corrected significance level of 0.008 to account for an inflated risk of type I error due to multiple testing (i.e. a total of 6 tests for the 6 difference flavonoid variables). Given the findings observed in Table 5, we also analyzed flavonoids from food sources only for each of the histological types. The findings were similar to that observed for flavonoids from all sources, except for total flavonoid intake where a statistically significant difference between histological types was observed, reflecting a significant inverse association with squamous cell carcinoma but not adenocarcinoma or small cell carcinoma (Table 6).

In sensitivity analyses to assess the potential for information bias by respondent status (proxy versus self), we restricted analyses to self-respondents only. The pattern of association across quartiles was the same for all 6 flavonoid variables; the adjusted ORs (95% CIs) for the highest versus the lowest quartiles were 0.84 (0.61-1.15) for anthocyanidin intake, 1.03 (0.77-1.39) for flavan-3-ol intake, 0.65 (0.47-0.89) for flavone intake, 0.97 (0.72-1.30) for flavonol intake, 0.69 (0.50-0.95) for flavanone intake, and 0.94 (0.72-1.22) for total flavonoid intake. We also conducted analyses where smoking was adjusted for more conventionally using the three variables of smoking status (ever smoker, never smoker), cigarette-years, and time since quitting (in years), rather than the CSI, and the results were not appreciably different (results not shown). Because our FFQ was specifically designed to capture foods rich in carotenoids and vitamin C, which are correlated with flavonoids in food, we further evaluated the potential confounding effect of total carotenoid intake and vitamin C intake. Adjusting for total carotenoid intake did

not substantially affect the results (not shown). However, after adjusting for vitamin C intake, the inverse associations with flavones and flavanones were attenuated. The adjusted OR (95% CI) for the highest versus the lowest quartiles of intake was 0.76 (0.54-1.06) for flavone intake and 0.79 (0.54-1.16) for flavanone intake. In these models, the association between vitamin C intake and lung cancer risk was also attenuated (data not shown).

DISCUSSION

Using data from a large, population-based case-control study, we observed that low intake of flavonoids from foods, but not from beverages, was associated with a higher risk of lung cancer overall. There was some suggestion that the inverse association with flavonoids, particularly for flavones and flavanones, was greater for squamous cell carcinoma than for adenocarcinoma or small cell carcinoma. Our results suggest that low flavonoid intake from food sources may increase risk of lung cancer, particularly for squamous cell carcinoma.

Previous studies have provided mixed evidence for a possible inverse association between dietary flavonoid intake and lung cancer. However, most studies used food composition databases that were more limited than the recent USDA database. Of the studies that did not use the recent USDA database for flavonoids, findings have been about evenly split between an inverse association (11-15) and no association (17-20, 22, 24). Among studies using the recent 2003 USDA database, Lagiou et al reported an increased lung cancer risk with increased flavonol intake, and no association with either flavanones or flavan-3-ols (23). In contrast, a Finnish cohort study reported a strong inverse association with increased intakes of flavonols and flavan-3-ols, though no association for the remaining 3 subclasses (16). Of the two previous

North American studies, one prospective study reported reduced lung cancer risks of 32% with flavanone intake (21), while in another case-control study, intake of flavan-3-ols, as well as quercetin and kaempferol, which are both flavonols, were associated with risk reductions of 32% to 51%, particularly among smokers (10).

As in the two recent North American studies that used the 2003 USDA database, we observed reduced lung cancer risks associated with increasing intake of certain flavonoid subclasses. On the other hand, the associations we observed for flavonols, flavan-3-ols and total flavonoids were non-monotonic; using the lowest intake quartile as the reference, the relative risk dipped in the middle range of intake and then increased in the highest intake quartile to reach levels similar to the lowest quartile. We further observed that the pattern of associations differed between flavonoids from food versus beverage sources. These various findings are compatible with the hypothesis that another component in flavonoid-rich foods (not present in beverages) is responsible for these inverse associations among food source flavonoids. For instance, we found that associations were attenuated when vitamin C was included as a covariate in the analyses. In two previous studies that included vitamin C in their models, an association with flavonoids was not observed (18, 19). Our study was not large enough to tease out the potential relative contributions of intercorrelated measures of flavonoids and vitamin C intake.

Alternatively, the differences between food and beverage sources may reflect the effects of other non-flavonoid nutrients found in wine, beer and tea, such as alcohol in wine and beer, or caffeine in tea, that may increase lung cancer risk. The non-monotonic relationship between lung cancer and intake of flavan-3-ols, flavonols and total flavonoids may reflect the balance between the

possible protective effect of flavonoids and the potential carcinogenic effects of other components of beverages (i.e. alcohol, caffeine), particularly at high intakes. Indeed, there is some evidence that high alcohol intake increases lung cancer risk in our study population (29). Black tea, which contributes heavily to flavan-3-ols and flavonols, has been associated both positively and negatively with lung cancer (42). Caffeine is a nutrient present in tea, but not in beer or wine, that may contribute to an increased risk, though there is currently little evidence for the carcinogenicity of caffeine (43). Variation in tea brewing time up to 5 minutes may influence flavonoid content (44). In addition, the main flavan-3-ols in tea [(-)-epigallocatechin gallate and (-)-epicatechin gallate] differ from the main flavan-3-ols found in foods [(+)-catechin and (-)-epicatechin], which may have contributed to the observed differences between foods and beverages. Furthermore, the differences may reflect variations in bioavailability or metabolism of the flavonoids in solid foods versus liquid beverages (45). On the other hand, these differences may reflect residual confounding, uncontrolled confounding by an unmeasured factor or possibly differential measurement error in determining intakes of beverages versus foods.

With 1,061 cases and 1,425 controls, this study represents the largest study examining flavonoid intake and lung cancer risk using the recent USDA food composition database. This sample size allowed us to examine potential effect modification by sex and smoking and to conduct separate analyses by histological type. We did not find statistically significant evidence of effect modification by smoking level, though reduced risks in the middle quartiles of intake of total flavonoids, flavan-3-ols and flavonols were more apparent among moderate-heavy smokers compared to never-light smokers. Among previous studies that have examined the potential modifying effect of smoking, most (10, 21, 22), but not all (46), have observed a stronger inverse

association among heavy smokers. It has been suggested that a stronger protective effect among smokers may be due to the biological mechanism of flavonoids, which may have strong antioxidant activity against the oxidative stress that results from smoking (10, 21). Only one other study presented results according to histology (22), and similar to our findings, they observed that inverse associations were stronger for squamous cell carcinoma and other histologies combined, compared to adenocarcinomas. Given that adenocarcinoma is the histological type that is most weakly associated with smoking (2), this observation may reflect that flavonoids play more of a protective role among those cancers more strongly associated with smoking.

Cases and controls were selected from the same study base, representing Canadian citizens residing in the greater Montreal area, and participation rates were relatively high, even among controls (70%). Nonetheless, it is possible that participating controls were not representative of all eligible controls with respect to diet. Differential reporting of diet by cases and controls may also have produced a bias in our results, as in any case-control study. There is undoubtedly some degree of misclassification in any attempt to measure nutrient intake on the basis of a FFQ, including ours. Such error would likely be non-differential with respect to case-control status, and thus, would have attenuated the strength of any true associations. Using proxy respondents for some participants may also have resulted in exposure misclassification, although our results were almost identical when restricted to self-respondents.

A major concern in epidemiological studies of lung cancer is the potential for residual confounding by smoking. For instance, it is possible that the reference groups of low flavonoid

intake may include individuals with higher levels of smoking. However, we controlled for various measures of smoking, including smoking status, duration of smoking, time since cessation and smoking intensity, incorporated into one parsimonious measure (i.e. the CSI)] (40). Only one previous study adjusted for time since quitting among former smokers (20), which is a factor that strongly impacts lung cancer risk (47, 48). We also had detailed information on other important potential confounders, including occupational carcinogens.

The FFQ used in the study was designed to capture carotenoids and vitamin C, thus, did not include some flavonoid-rich items. For instance, onion, a major contributor to flavonols, was not assessed on our FFQ thus intake of the flavonol subclass was likely underestimated for all participants. Similarly, celery and parsley, major contributors to flavones (34) were not assessed thus leading to underestimation of flavone intake. Nonetheless, intake of flavonoid subclasses in our study was similar to previous studies that used the USDA flavonoids database (10, 16, 21, 23). Unfortunately, since soy, tofu and other isoflavone-rich foods, such as chickpeas and peanuts, were not included on our FFQ, we were not able to capture a large contrast in isoflavone intake in our study population, thus precluding a comprehensive analysis. However, our FFQ assessed citrus fruits, berries, tea and wine, which are the main contributors to flavanones, flavon-3-ols and anthocyanidins, and which are flavonoid subclasses not extensively examined previously. Indeed, tea, wine and beer are not major contributors to carotenoids and vitamin C, thus, our analysis of flavonoids captures a different aspect of diet than the analysis of carotenoids and vitamin C, or of alcohol or tea.

In summary, our results suggest that low flavonoid intake from food sources may increase the risk of lung cancer, particularly for squamous cell carcinoma. While smoking remains the most important factor associated with lung cancer risk, the identification of other modifiable factors can offer additional avenues for lung cancer prevention.

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Table 1. Characteristics of the study population, n (%)

	Women		Men	
	Cases N =399	**Controls N =574**	**Cases N =662**	**Controls N=851**
Age, years				
<45	22 (5.5)	33 (5.8)	13 (2.0)	17 (2.0)
45-<55	73 (18.3)	115 (20.0)	71 (10.7)	83 (9.8)
55-<65	138 (34.6)	183 (31.9)	218 (32.9)	246 (28.9)
65+	166 (41.6)	243 (42.3)	360 (54.4)	505 (59.3)
Respondent status				
Self	272 (68.2)	548 (95.5)	416 (62.8)	771 (90.6)
Proxy	127 (31.8)	26 (4.5)	246 (37.2)	80 (9.4)
Ethnic origin				
French ancestry	315 (79.0)	397 (69.2)	516 (78.0)	545 (64.0)
Other	84 (21.0)	177 (30.8)	146 (22.0)	306 (36.0)
BMI, kg/m^2				
Underweight (<18.5)	34 (8.5)	19 (3.3)	25 (3.8)	10 (1.2)
Normal weight (18.5-<25.0)	206 (51.6)	270 (47.0)	315 (47.6)	335 (39.4)
Overweight (25.0-<30.0)	112 (28.1)	205 (35.7)	242 (36.6)	394 (46.3)
Obese (30.0+)	47 (11.8)	80 (14.0)	80 (12.1)	112 (13.2)
Mean census tract family income, $[1]				
Low	189 (47.4)	192 (33.4)	258 (39.0)	288 (33.8)
Middle	135 (33.8)	191 (33.3)	211 (31.9)	280 (32.9)
High	75 (18.8)	191 (33.3)	193 (29.2)	283 (33.3)
Education level, years				
<7	85 (21.3)	95 (16.6)	186 (28.1)	212 (24.9)
7-<13	238 (59.7)	271 (47.2)	373 (56.3)	405 (47.6)
13+	76 (19.0)	208 (36.2)	103 (15.6)	234 (27.5)
Daily Alcoholic Drinks				
Non-drinker	335 (84.0)	497 (86.6)	368 (55.6)	535 (62.9)
>0 to <2 standard drinks	30 (7.5)	54 (9.4)	56 (8.4)	81 (9.5)
2 + standard drinks	34 (8.5)	23 (4.0)	238 (36.0)	235 (27.6)
Cigarette Smoking				
Never	31 (7.8)	294 (51.2)	16 (2.4)	151 (17.7)
Former (quit 10+ years ago)	42 (10.5)	109 (19.0)	137 (20.7)	381 (44.8)
Former (quit 2-<10 years ago)	36 (9.0)	46 (8.0)	65 (9.8)	79 (9.3)
Current[2]	290 (72.7)	125 (21.8)	444 (67.1)	240 (28.2)
Histological type				
Adenocarcinoma	193 (48.4)	--	219 (33.1)	--
Squamous cell carcinoma	78 (19.6)	--	234 (35.4)	--
Small cell carcinoma	67 (16.8)	--	111 (16.8)	--
Large cell carcinoma	35 (8.8)	--	64 (9.7)	--
Other or unspecified	26 (6.5)	--	34 (5.1)	--

1 Low, medium and high correspond to sex-specific tertiles based on the distribution among controls

2 Current smokers include individuals that quit <2 years before recruitment

Table 2. Food and beverage items that primarily contributed to flavonoid intake in the study population

	Primary contributors (percent contribution to intake)[1]	
	Food	Beverage
Total flavonoids	Citrus fruits (8%) Apples/pears (4%) Berries (2%)	Black tea (70%) Citrus juices (8%)
Anthocyanidins	Berries (46%) Apples/pears (22%)	Red wine (22%)
Flavan-3-ols	Apples/pears (2%)	Black tea (92%) Beer (2%) Red wine (2%)
Flavones	Citrus fruits (32%) Lettuce (12%) Watermelon (8%)	Red wine (28%)
Flavonols	Apples/pears (16%) Lettuce (8%)	Black tea (36%) Beer (12%)
Flavanones	Citrus fruits (62%)	Citrus juices (34%) Red wine/white wine (2%)

1 The denominator for the percent contribution includes total intake of the flavonoid subclass in the study population from both food and beverage

Table 3. Odds ratios (95% confidence intervals) of lung cancer for quartiles of flavonoid intake

	Quartile of intake[1]			
	1	**2**	**3**	**4**
Total flavonoids				
#cases/#controls	396/355	172/357	175/356	318/357
OR (95% CI)[2]	1.00	0.43 (0.34-0.54)	0.51 (0.40-0.63)	0.83 (0.67-1.03)
OR (95% CI)[3]	1.00	0.64 (0.48-0.85)	0.76 (0.57-1.02)	0.94 (0.72-1.22)
Anthocyanidins, total				
#cases/#controls	451/357	236/356	182/357	192/355
OR (95% CI)[2]	1.00	0.52 (0.42-0.65)	0.40 (0.32-0.50)	0.43 (0.34-0.54)
OR (95% CI)[3]	1.00	0.97 (0.73-1.27)	0.70 (0.53-0.94)	0.87 (0.65-1.16)
Flavan-3-ols, total				
#cases/#controls	311/357	174/356	251/357	325/355
OR (95% CI)[2]	1.00	0.56 (0.44-0.71)	0.81 (0.65-1.01)	1.07 (0.86-1.33)
OR (95% CI)[3]	1.00	0.91 (0.67-1.22)	0.83 (0.61-1.13)	1.06 (0.81-1.39)
Flavones, total				
#cases/#controls	498/357	210/356	186/357	167/355
OR (95% CI)[2]	1.00	0.42 (0.34-0.53)	0.38 (0.30-0.47)	0.34 (0.27-0.43)
OR (95% CI)[3]	1.00	0.63 (0.48-0.84)	0.67 (0.51-0.89)	0.67 (0.50-0.91)
Flavonols, total				
#cases/#controls	329/357	212/356	201/357	319/355
OR (95% CI)[2]	1.00	0.65 (0.52-0.81)	0.61 (0.49-0.77)	0.99 (0.80-1.22)
OR (95% CI)[3]	1.00	0.76 (0.57-1.01)	0.66 (0.49-0.88)	0.98 (0.74-1.28)
Flavanones, total				
#cases/#controls	461/357	268/356	156/357	176/355
OR (95% CI)[2]	1.00	0.58 (0.47-0.72)	0.34 (0.27-0.43)	0.39 (0.31-0.49)
OR (95% CI)[3]	1.00	0.94 (0.71-1.23)	0.61 (0.45-0.82)	0.69 (0.52-0.93)

1 Quartile cut points for total intake are based on flavonoid intake adjusted for total energy using the residual method and are as follows (in mg/day): Anthocyanidin: Female <8.0, 8.0-<10.8, 10.8-<15.4, 15.4+, Male <6.6, 6.6-<13.3, 13.3-<23.1, 23.1+; Flavan-3-ols: Female <8.7, 8.7-<14.8, 14.8-<249.1, 249.1+, Male <12.6, 12.6-<24.8, 24.8-<271.0, 271.0+; Flavones: Female <0.6, 0.6-<0.9, 0.9-<1.4, 1.4+, Male <0.7, 0.7-<1.3, 1.3-<2.1, 2.1+; Flavonols: Female <7.6, 7.6-<11.0, 11.0-<16.6, 16.6+, Male: <11.7, 11.7-<16.7, 16.7-<24.3, 24.3+; Flavanones: Female <18.7, 18.7-<32.3, 32.3-<50.3, 50.3+, Male: <20.8, 20.8-<44.0, 44.0-<64.6, 64.6+.

2 ORs are adjusted for age and sex

3 ORs are adjusted for age, sex, number of school years (<7, 7-<13, 13+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), respondent status (self, proxy), comprehensive smoking indicator (continuous), occupational exposure to carcinogens (none, ever), BMI (underweight, normal weight, overweight, obese), number of alcoholic drinks/day (continuous) and total energy intake (continuous)

Table 4. Adjusted odds ratios[1] (95% confidence intervals) between lung cancer and total intake of flavonoids and flavonoid subclasses, stratified by sex and by smoking

	Quartile of intake				P (int)[2]
	1	2	3	4	
By Sex					
Total flavonoids					
Male	1.00	0.68 (0.47-0.98)	0.73 (0.50-1.05)	1.01 (0.73-1.40)	
Female	1.00	0.57 (0.34-0.95)	0.85 (0.52-1.42)	0.77 (0.48-1.22)	0.66
Anthocyanidins, total					
Male	1.00	1.32 (0.94-1.87)	0.92 (0.64-1.31)	0.97 (0.66-1.44)	
Female	1.00	0.55 (0.34-0.90)	0.43 (0.26-0.71)	0.74 (0.46-1.18)	<0.01
Flavan-3-ols, total					
Male	1.00	0.98 (0.67-1.43)	0.95 (0.64-1.41)	1.18 (0.84-1.67)	
Female	1.00	0.80 (0.48-1.33)	0.75 (0.44-1.26)	0.85 (0.53-1.35)	0.60
Flavones, total					
Male	1.00	0.65 (0.46-0.91)	0.61 (0.42-0.88)	0.67 (0.45-0.99)	
Female	1.00	0.58 (0.35-0.96)	0.79 (0.49-1.28)	0.67 (0.41-1.11)	0.68
Flavonols, total					
Male	1.00	0.79 (0.55-1.13)	0.67 (0.46-0.97)	1.14 (0.81-1.60)	
Female	1.00	0.79 (0.48-1.30)	0.67 (0.41-1.11)	0.75 (0.47-1.20)	0.69
Flavanones, total					
Male	1.00	0.98 (0.70-1.37)	0.60 (0.41-0.89)	0.67 (0.46-0.97)	
Female	1.00	0.83 (0.52-1.35)	0.53 (0.32-0.89)	0.63 (0.39-1.03)	0.49
By Smoking Level[3]					
Total flavonoids					
Never-light	1.00	0.60 (0.32-1.10)	1.12 (0.66-1.91)	0.74 (0.43-1.27)	
Moderate-heavy	1.00	0.63 (0.45-0.89)	0.62 (0.44-0.89)	0.99 (0.73-1.34)	0.40
Anthocyanidins, total					
Never-light	1.00	1.03 (0.58-1.82)	0.96 (0.54-1.72)	1.14 (0.65-1.99)	
Moderate-heavy	1.00	0.96 (0.70-1.33)	0.65 (0.47-0.91)	0.77 (0.54-1.09)	0.97
Flavan-3-ols, total					
Never-light	1.00	1.29 (0.73-2.29)	1.59 (0.86-2.92)	1.01 (0.56-1.81)	
Moderate-heavy	1.00	0.80 (0.56-1.14)	0.69 (0.48-1.00)	1.08 (0.79-1.49)	0.46
Flavones, total					
Never-light	1.00	0.54 (0.30-0.98)	0.68 (0.38-1.21)	0.84 (0.48-1.46)	
Moderate-heavy	1.00	0.66 (0.47-0.91)	0.67 (0.48-0.93)	0.57 (0.40-0.82)	0.20
Flavonols, total					
Never-light	1.00	1.26 (0.72-2.22)	1.26 (0.71-2.23)	0.93 (0.53-1.64)	
Moderate-heavy	1.00	0.65 (0.46-0.91)	0.54 (0.38-0.77)	1.00 (0.72-1.38)	0.24
Flavanones, total					
Never-light	1.00	0.76 (0.44-1.32)	0.57 (0.32-1.02)	0.58 (0.33-1.02)	
Moderate-heavy	1.00	1.02 (0.74-1.41)	0.61 (0.43-0.87)	0.71 (0.50-1.01)	0.44

1 ORs adjusted for the same variables indicated in footnote 3 of table 3

2 P-value for the test for interaction; the test for interaction by smoking level used the comprehensive smoking indicator (CSI)

3 Never-light smokers includes lifetime never smokers combined with people in the lowest quartile of the CSI among ever smokers (n=134 cases, 857 controls); Moderate-heavy smokers are those in the upper three quartile of the CSI among ever smokers (n=927 cases, 568 controls)

Table 5. Adjusted odds ratios[1] (95% confidence intervals) between lung cancer and total intake of flavonoids and flavonoid subclasses, by dietary source of flavonoids

	Quartile of intake			
	1	**2**	**3**	**4**
Total flavonoids				
Beverage sources only	1.00	0.97 (0.71-1.32)	1.12 (0.81-1.55)	1.19 (0.87-1.63)
Food sources only	1.00	0.64 (0.49-0.84)	0.62 (0.47-0.83)	0.63 (0.47-0.85)
Anthocyanidins				
Beverage sources only	1.00	0.96 (0.69-1.34)	1.10 (0.75-1.61)	1.10 (0.75-1.62)
Food sources only	1.00	1.05 (0.80-1.38)	0.81 (0.61-1.09)	0.82 (0.61-1.11)
Flavan-3-ols				
Beverage sources only	1.00	1.00 (0.73-1.37)	1.03 (0.74-1.44)	1.17 (0.85-1.59)
Food sources only	1.00	0.87 (0.66-1.15)	0.75 (0.56-1.01)	0.67 (0.50-0.90)
Flavones				
Beverage sources only	1.00	0.96 (0.69-1.34)	1.10 (0.75-1.61)	1.10 (0.75-1.62)
Food sources only	1.00	0.72 (0.54-0.94)	0.70 (0.52-0.93)	0.68 (0.50-0.93)
Flavonols				
Beverage sources only	1.00	0.99 (0.73-1.35)	1.00 (0.73-1.38)	1.13 (0.83-1.55)
Food sources only	1.00	0.89 (0.68-1.15)	0.64 (0.48-0.87)	0.62 (0.45-0.84)
Flavanones				
Beverage sources only	1.00	0.96 (0.69-1.34)	1.10 (0.75-1.61)	1.10 (0.75-1.62)
Food sources only	1.00	0.97 (0.74-1.27)	0.60 (0.44-0.81)	0.70 (0.53-0.94)

1 ORs adjusted for the same variables indicated in footnote 3 of table 3

Table 6. Adjusted odds ratios[1] (95% confidence intervals) between each of three histologic types[2] of lung cancer and intake of flavonoids and flavonoid subclasses from all sources and food sources only

	Quartile of intake				P (het)[3]
	1	2	3	4	
Total flavonoids, all sources					
Adenocarcinoma	1.00	0.75 (0.52-1.08)	0.87 (0.60-1.26)	1.09 (0.78-1.51)	
Squamous cell carcinoma	1.00	0.55 (0.36-0.85)	0.60 (0.39-0.92)	0.92 (0.65-1.30)	
Small cell carcinoma	1.00	0.53 (0.30-0.92)	1.00 (0.60-1.68)	0.80 (0.50-1.25)	0.12
Anthocyanidins, all sources					
Adenocarcinoma	1.00	1.04 (0.74-1.47)	0.74 (0.52-1.07)	0.93 (0.65-1.34)	
Squamous cell carcinoma	1.00	0.89 (0.61-1.30)	0.59 (0.39-0.89)	0.75 (0.49-1.13)	
Small cell carcinoma	1.00	0.99 (0.61-1.61)	0.77 (0.47-1.28)	1.01 (0.59-1.73)	0.76
Flavan-3-ols, all sources					
Adenocarcinoma	1.00	1.15 (0.79-1.69)	1.02 (0.69-1.52)	1.35 (0.95-1.90)	
Squamous cell carcinoma	1.00	0.73 (0.47-1.13)	0.67 (0.43-1.04)	0.98 (0.68-1.41)	
Small cell carcinoma	1.00	0.74 (0.43-1.28)	0.65 (0.37-1.14)	0.78 (0.49-1.25)	0.22
Flavones, all sources					
Adenocarcinoma	1.00	0.72 (0.50-1.02)	0.84 (0.59-1.20)	0.86 (0.59-1.25)	
Squamous cell carcinoma	1.00	0.59 (0.40-0.85)	0.42 (0.27-0.65)	0.48 (0.31-0.75)	
Small cell carcinoma	1.00	0.54 (0.33-0.89)	0.72 (0.43-1.19)	0.65 (0.36-1.15)	<0.01
Flavonols, all sources					
Adenocarcinoma	1.00	0.88 (0.61-1.28)	0.87 (0.60-1.26)	1.18 (0.83-1.67)	
Squamous cell carcinoma	1.00	0.69 (0.46-1.04)	0.46 (0.30-0.71)	0.93 (0.65-1.35)	
Small cell carcinoma	1.00	0.67 (0.40-1.11)	0.56 (0.32-0.96)	0.75 (0.47-1.21)	0.08
Flavanones, all sources					
Adenocarcinoma	1.00	0.92 (0.65-1.30)	0.68 (0.47-1.00)	0.89 (0.62-1.27)	
Squamous cell carcinoma	1.00	0.74 (0.51-1.07)	0.54 (0.35-0.82)	0.48 (0.32-0.74)	
Small cell carcinoma	1.00	1.20 (0.76-1.91)	0.51 (0.28-0.93)	0.70 (0.41-1.20)	0.02
Total flavonoids, food sources					
Adenocarcinoma	1.00	0.69 (0.48-0.97)	0.86 (0.60-1.22)	0.78 (0.53-1.14)	
Squamous cell carcinoma	1.00	0.56 (0.39-0.82)	0.53 (0.35-0.81)	0.43 (0.27-0.68)	
Small cell carcinoma	1.00	0.73 (0.46-1.15)	0.44 (0.25-0.79)	0.60 (0.34-1.07)	<0.01
Anthocyanidins, food sources					
Adenocarcinoma	1.00	1.10 (0.78-1.56)	0.94 (0.66-1.35)	0.89 (0.61-1.30)	
Squamous cell carcinoma	1.00	1.11 (0.77-1.60)	0.69 (0.46-1.04)	0.68 (0.44-1.06)	
Small cell carcinoma	1.00	1.03 (0.63-1.66)	0.67 (0.39-1.14)	1.09 (0.65-1.85)	0.36
Flavan-3-ols, food sources					
Adenocarcinoma	1.00	0.86 (0.61-1.22)	0.82 (0.57-1.17)	0.77 (0.53-1.13)	
Squamous cell carcinoma	1.00	0.92 (0.63-1.33)	0.66 (0.43-1.00)	0.58 (0.38-0.89)	
Small cell carcinoma	1.00	0.95 (0.59-1.55)	0.85 (0.50-1.44)	0.73 (0.42-1.27)	0.52
Flavones, food sources					
Adenocarcinoma	1.00	0.82 (0.57-1.16)	0.88 (0.62-1.26)	0.82 (0.56-1.21)	
Squamous cell carcinoma	1.00	0.70 (0.49-1.02)	0.41 (0.27-0.64)	0.51 (0.33-0.80)	
Small cell carcinoma	1.00	0.69 (0.42-1.12)	0.72 (0.43-1.20)	0.52 (0.28-0.97)	<0.01
Flavonols, food sources					
Adenocarcinoma	1.00	0.91 (0.65-1.26)	0.85 (0.58-1.23)	0.70 (0.47-1.04)	
Squamous cell carcinoma	1.00	0.82 (0.57-1.17)	0.50 (0.32-0.79)	0.50 (0.32-0.79)	
Small cell carcinoma	1.00	0.83 (0.53-1.30)	0.56 (0.32-0.99)	0.49 (0.27-0.92)	0.08
Flavanones, food sources					
Adenocarcinoma	1.00	0.92 (0.65-1.30)	0.68 (0.47-1.00)	0.88 (0.61-1.27)	
Squamous cell carcinoma	1.00	0.80 (0.55-1.16)	0.50 (0.32-0.77)	0.51 (0.33-0.77)	
Small cell carcinoma	1.00	1.24 (0.78-1.96)	0.51 (0.28-0.91)	0.67 (0.39-1.17)	0.03

1 ORs adjusted for the same variables indicated in footnote 3 of table 3

2 n=412 cases of adenocarcinoma, 312 cases of squamous cell carcinoma and 178 cases of small cell carcinoma

3 p-value for the likelihood ratio test of homogeneity of the ORs across histological types, which compared the deviance of two polytomous logistic models; the first, un-restricted model used 9 degree-of-freedom (df; 3 histologic type-specific parameters for each of the 3 higher quartiles) while the restricted, second model used only 3 df's (1 common parameter for each quartile), resulting in a 6-df difference for the likelihood ratio test