**Intake of Flavonoids and Lung Cancer**

Loïc Le Marchand, Suzanne P. Murphy, Jean H. Hankin, Lynne R. Wilkens, Laurence N. Kolonel

**Background:** To investigate the possible relationship between intake of flavonoids—powerful dietary antioxidants that may also inhibit P450 enzymes—and lung cancer risk, we conducted a population-based, case-control study in Hawaii.

**Methods:** An in-person interview assessed smoking history and usual intake of 242 food items for 582 patients with incident lung cancer and 582 age-, sex-, and ethnicity-matched control subjects. Subjects who donated a blood sample were genotyped for the P450 enzyme variant allele CYP1A1*2 by use of a polymerase chain reaction-based method. Logistic regression analysis was used to compute odds ratios (ORs) and 95% confidence intervals (CIs). All P values are two-sided.

**Results:** After adjusting for smoking and intakes of saturated fat and β-carotene, we found statistically significant inverse associations between lung cancer risk and the main food sources of the flavonoids quercetin (onions and apples) and naringin (white grapefruit). The lung cancer OR for the highest compared with the lowest quartile of intake was 0.5 (95% CI = 0.3–0.9) for onions (P for trend = .001) and 0.6 (95% CI = 0.4–1.0) for apples (P for trend = .03). The OR for the highest compared with the lowest tertile of intake for white grapefruit was 0.5 (95% CI = 0.2–0.9) (P for trend = .02). No association was found for important food sources of other flavonoids. Using published food-composition data for flavonoids, we found an inverse association between intake of quercetin and risk of lung cancer (P for trend = .07) that appears consistent with associations for its food sources. The effect of onions was particularly strong against squamous cell carcinoma (a cell type specifically associated with CYP1A1*2 in our study) and was modified by the CYP1A1 genotype, suggesting that CYP1A1 may play a role in this association.

**Conclusion:** If replicated, particularly in prospective studies, these findings would suggest that foods rich in certain flavonoids may protect against certain forms of lung cancer and that decreased bioactivation of carcinogens by inhibition of CYP1A1 should be explored as underlying mechanisms. [J Natl Cancer Inst 2000; 92:154–60]

Intake of vegetables and fruits has consistently been associated with a reduced risk of lung cancer (1). Although many constituents of these foods have shown anticarcinogenic activity in the laboratory, only a few have been widely studied in humans. Because β-carotene had been inversely associated with lung cancer in various populations (1), this nutrient was selected early on for chemoprevention trials among individuals at high risk (smokers and asbestos-exposed workers) or low risk (U.S. physicians) for lung cancer (2–5). The results of these large trials have been disappointing because they showed no beneficial effect (3), and even—in high-risk individuals—a detrimental effect on lung cancer incidence (4, 5). α-Tocopherol supplementation also failed to prevent lung cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (4).

It has been stressed for some time that the association with β-carotene in observational studies is difficult to distinguish from that of vegetables and fruits and that, indeed, similar associations could be demonstrated between lung cancer and other plant constituents. For example, in a case-control study in Hawaii, we found inverse associations with total intake of vegetables and subgroups of vegetables rich in other phytochemicals (dark-green vegetables, cruciferous vegetables, tomatoes, and carrots) that were stronger than those for β-carotene (6) and other specific carotenoids (7). Recent literature reviews and more recent studies of diet and lung cancer (8–12) have further emphasized the need to consider various components of fruits and vegetables as risk factors for this disease.

Flavonoids are polyphenolic compounds that occur ubiquitously in foods and beverages of plant origin (13). They are strong antioxidants by efficiently scavenging free radicals (14–16) that are thought to be involved in DNA damage and tumor promotion (17). Quercetin and other related flavonoids inhibit carcino-gen-induced tumors in rodents (18,19). One of the possible mechanisms for this protective effect is the well-documented ability of some flavonoids, such as quercetin and naringenin (the aglycone derived from naringin), to inhibit certain cytochrome P450 enzymes (CYP1A1 and CYP3A4, respectively) involved in the bioactivation of chemical carcinogens (20).

We report here on the associations between intake of flavonoids and lung cancer risk in a population-based, case-control study conducted in Hawaii. Because only limited food-composition data are yet available for flavonoids, we made an a priori decision to give greater emphasis to food sources in the interpretation of the data. We also examined the modifying effect of a common polymorphism in the CYP1A1 gene on these associations in an effort to identify underlying mechanisms.

**METHODS**

**Study Population**

The human subjects protocol for this study was reviewed and approved by the Committee on Human Studies of the University of Hawaii and by the institutional review board of each participating hospital. Lung cancer patients were identified by the rapid-reporting system of the Hawaii Tumor Registry, a member of the Surveillance, Epidemiology, and End Results (SEER)1 Program of the National Cancer Institute. Eligible case patients were all patients with histologically confirmed primary lung cancer who were newly diagnosed during the period from January 1, 1992, through March 31, 1997, in all main medical centers on the island of Oahu, HI. Other eligibility criteria included age between 26 and 79 years, Oahu residency, no history of lung cancer, and appropriate ethnicity (at least 75% ethnically Asian, at least 75% Caucasian of European descent, or any percentage Hawaiian/part-Hawaiian heritage). Histologic information was abstracted directly from each patient’s pathology report. An interview was completed for 64% (375 men and 207 women) of the eligible case patients. The main reasons for nonparticipation were patient refusal (17%), physician refusal (2%), and death with absence of a suitable surrogate for interview (17%). Interviewed case patients were more likely to be Hawaiian (25% versus 19%), were less likely to have a distant metastasis (37% versus 50%), and were younger by an average of 1 year compared with noninterviewed cases.

**Affiliation of authors:** Etiology Program, Cancer Research Center of Hawaii, University of Hawaii, Honolulu.

**Correspondence to:** Loïc Le Marchand, M.D., Ph.D., Etiology Program, Cancer Research Center of Hawaii, University of Hawaii, 1236 Lauhala St., Suite 407, Honolulu, HI 96813 (e-mail: loc@crch.hawaii.edu).

See “Notes” following “References.”

© Oxford University Press
Control subjects were selected randomly from a list of Oahu residents interviewed by the State of Hawaii Department of Health as part of a health survey of a 2% random sample of state households. This source was supplemented with control subjects from Health Care Finance Administration participants on Oahu. One control subject was matched to each case patient on the basis of sex, ethnicity (within the three categories defined above), and age (±2 years). The overall participation rate for the control subjects was 62%. Reasons for nonparticipation included refusal (25%), inability to locate (10%), serious illness (1%), and death (2%). Compared with noninterviewed control subjects, interviewed control subjects were similar in their sex and race distribution but were slightly younger (mean age: 65.5 years versus 66.5 years). When possible, a proxy interview was obtained from the next of kin for subjects who were deceased or too ill (28.5% of case patients and 2.9% of control subjects). A blood sample was collected from 76% of interviewed case patients and from 80% of interviewed control subjects. There were no differences in the age, sex, and race distributions of control subjects who gave blood compared with those who did not. However, case patients who gave blood were younger by an average of 1 year and were less likely to have a distant metastasis than those who declined the blood donation.

Trained interviewers conducted in-person interviews at the subjects’ homes. Fifty percent of case patients were interviewed within 3.5 months, and 88% were interviewed within 6.0 months of diagnosis. Written informed consent was obtained from each participant. The questionnaire included detailed demographic information, such as ethnic origin of each grandparent, a lifetime history of tobacco and alcohol use, a quantitative food-frequency questionnaire, and a personal history of exposure to environmental tobacco smoke, various relevant medical conditions and occupational exposures, and a family history of lung diseases. Information was collected on the types (nonfiltered cigarettes, filtered cigarettes, cigars, and pipes) of tobacco products ever smoked daily for at least 6 months and, for each tobacco product, the usual amount smoked per day, the age when smoking started, the overall duration of use, and, for ex-smokers, the age when smoking stopped. We also inquired about any periods of smoking cessation for each tobacco product during the subject’s life. Smokers were considered current smokers if they smoked up to 1 year before the date of diagnosis for case patients or up to the date of interview for control subjects. In the analysis, cigarettes, pipes, and cigars were treated equivalently.

**Food-Frequency Analysis**

The food-frequency questionnaire used in this study (21) has been validated previously in our population and was designed to capture total dietary intake (22). Frequencies and amounts consumed were sought for 242 food items or categories. The reference period for the dietary questionnaire was the year before diagnosis for case patients or before interview for control subjects. If a change had occurred in the types and amounts of foods consumed in the 3 years preceding diagnosis (for case patients) or interview (for control subjects), the reference period was the year before the change. For seasonal foods, the reference period was limited to the time period during which each food was available. Collected photographs of most food items, showing three different portion sizes, as well as measuring cups and spoons, were used in the interview to facilitate quantification of intakes.

Daily intake in grams for each food item was computed for each individual. A food-composition nutrient database was applied to the items to assess nutrient intake. Individual nutrient intakes were calculated by summing across all food items. Gram amounts of particular food groups of interest were calculated by summing the grams for the foods or components of mixed dishes within that food category. The proportion of each mixed dish represented by a particular food was estimated from standard recipes. The food-composition data were based primarily on the U.S. Department of Agriculture’s (Washington, DC) nutrient database (23) and were supplemented with data from other research and commercial publications. Values for three flavonoids (quercetin, kaempferol, and myricetin) and two flavanone glycosides (hesperidin and naringin) for the foods on the diet questionnaire were obtained from the literature (24–34). If analytic data were unavailable for a food item, values were imputed from similar foods.

**CYP1A1 Genotyping**

Subjects were genotyped for a T→C substitution at the 3’ end of the CYP1A1 gene (CYP1A1*2 allele) that creates a MspI restriction site. This polymorphism is in linkage disequilibrium with a A→G transition in exon 7 that results in an Ile→Val change in the heme-binding domain of the protein and greater enzymatic activity (35). Laboratory personnel were blinded to the case–control status of the subjects. DNA extraction from blood lymphocytes and genotyping of subjects for the CYP1A1*2 allele were performed as described elsewhere (36).

**Statistical Methods**

In the statistical analysis, we used conditional logistic regression to compute odds ratios (ORs) and 95% confidence intervals (CIs) for quartiles or tertiles of daily nutrient and food intakes, with adjustment for relevant covariates (37). All reported P values are two-sided and considered to be statistically significant when less than .05. Linear dose-response was tested by entering in the model a trend variable assigned the median intake level for the quintile. Because the ORs from sex-specific analyses were very comparable, only the results for both sexes combined are presented to save space. The matched-pair design was not followed in analyses that included genotyping results because often only one member of the pair donated a blood sample. For those analyses, unconditional logistic regression was used, with further adjustment for the matching variables (age, sex, and ethnicity). Nutrient intakes were adjusted for caloric intake by use of the method of residuals (38). Several ways of modeling the smoking effect were explored and included separate categorization for duration and amount, use of a “pack-years” and an “age-started” term, logarithmic transformations of the variables, and addition of higher polynomial terms. The best fitting model was one that included an indicator variable for smoking status (ever smoked or never smoked) and separate continuous terms for duration, amount, and (duration)². The log-likelihood ratio test was used to test the statistical significance of modeled effects. We also used this test to determine interactions among certain variables with respect to lung cancer risk. The test compared main effects, no interaction model with a fully parameterized model containing all possible interaction terms for the variables of interest.

**RESULTS**

Thirty-eight percent of the subjects were Caucasians, 37% were ethnic Japanese, and 25% were Hawaiians. Table 1 presents relevant background characteristics of the lung cancer case patients and population control subjects. As expected, smoking was strongly associated with lung cancer risk. In addition and in agreement with past studies in this population (6,39), case patients were less educated and consumed more saturated fat and less β-carotene and vegetables.

<p>| Table 1. Distribution of lung cancer case patients and control subjects by selected characteristics |
|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, y</td>
<td>65.5</td>
<td>65.4</td>
<td>66.0</td>
<td>65.6</td>
</tr>
<tr>
<td>Education, mean, y</td>
<td>12.3</td>
<td>13.6</td>
<td>12.2</td>
<td>13.3</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>2.4</td>
<td>30.4</td>
<td>14.5</td>
<td>52.7</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>51.2</td>
<td>54.9</td>
<td>39.1</td>
<td>32.8</td>
</tr>
<tr>
<td>Current smoker</td>
<td>46.4</td>
<td>14.7</td>
<td>46.4</td>
<td>14.5</td>
</tr>
<tr>
<td>Pack-years, mean</td>
<td>64.9</td>
<td>26.9</td>
<td>42.7</td>
<td>13.9</td>
</tr>
<tr>
<td>Calories, mean, kcal/day</td>
<td>2967</td>
<td>2723</td>
<td>2221</td>
<td>2064</td>
</tr>
<tr>
<td>% calories from fat, mean</td>
<td>32.8</td>
<td>31.4</td>
<td>31.8</td>
<td>29.9</td>
</tr>
<tr>
<td>β-Carotene, mean, mg/day</td>
<td>3.8</td>
<td>5.7</td>
<td>5.4</td>
<td>6.3</td>
</tr>
<tr>
<td>Total vegetables, mean, g/day</td>
<td>277</td>
<td>346</td>
<td>270</td>
<td>311</td>
</tr>
</tbody>
</table>
CI for lung cancer by increasing intake of the main food sources of flavonoids, after adjustment for smoking and β-carotene and saturated fat intakes. Statistically significant inverse associations were found for onions, apples, and white grapefruit, with a 40%–50% decreased risk in the highest compared with the lowest category of intake. No clear association was observed for pink grapefruit; other citrus fruits, broccoli, celery, soy products, red wine, white wine, black tea, and green tea. Similarly, beer, hard liquor, and ethanol intakes were not associated with lung cancer risk in our data. Onions, apples, black tea, green tea, and red wine are important dietary sources of quercetin, whereas white grapefruit is a rich source of naringin. Because onions are also rich in potentially protective diallyl sulfides, we also estimated the lung cancer risk associated with intake of garlic, another allium vegetable. The OR by increasing quartile of garlic intake was 1.0 (referent), 0.9 (95% CI = 0.6–1.4), 0.8 (95% CI = 0.5–1.2), and 0.7 (95% CI = 0.4–1.1), and the P value for the trend test was .12. Given this weak association with garlic, we interpreted the effect for onions as being related more to the intake of quercetin than to the intake of diallyl sulfides.

The ORs for lung cancer by increasing intake of specific flavonoids and flavanones are shown in Table 2, B. Consistent with the associations in Table 2, A, we found a suggestion of an association with quercetin (P for trend = .07). Although not statistically significant (P for trend = .17), the risk pattern for naringin was also consistent with the inverse association observed with its main food source. There was no association with intake of the other flavonoids (kaempferol, myricetin, and hesperidin) and with the sum of the five flavonoids.

To examine the homogeneity of the results, we stratified our analysis of foods into tertiles of intake. No clear association was found for onions, apples, white grapefruit, quercetin, and naringin. The association with onions was clearly weaker for adenocarcinoma than for squamous cell carcinoma or the other cell types combined. The OR for adenocarcinoma for the highest compared with the lowest quartile of onion intake was 0.6 (95% CI = 0.3–1.2) (P for trend = .24). The corresponding OR for squamous cell carcinoma was 0.1 (95% CI = 0.0–0.6) (P for trend = .003).

Table 3 presents risk estimates for the main cell types of lung cancer by intake levels of onions, apples, white grapefruit, quercetin, and naringin. The association with onions was clearly weaker for adenocarcinoma than for squamous cell carcinoma or the other cell types combined. The OR for adenocarcinoma for the highest compared with the lowest quartile of onion intake was 0.6 (95% CI = 0.3–1.2) (P for trend = .24). The corresponding OR for squamous cell carcinoma was 0.1 (95% CI = 0.0–0.6) (P for trend = .003).

For the other foods and both flavonoids, the reduction in risk in the highest quintile was also greater for squamous cell carcinoma than for adenocarcinoma, although none of the ORs or trends was statistically significant (Table 3).

We tested the modifying effect of the CYP1A1 MspI polymorphism on the association between onions and lung cancer (Table 4). When we cross-classified the subset of subjects who donated a blood sample by their CYP1A1 genotype and onion intake, we found that the protective effect of onions against squamous cell carcinoma was about twofold greater in individuals with the homozygous wild-type genotype (CYP1A1*1/*1) than in those carrying the CYP1A1*2 variant allele, which suggests that the effect of onions was stronger for the low enzymatic activity (wild-type) genotype. Despite our limited sample size in this subgroup (72 case patients and 453 control subjects), the P for interaction was of borderline significance (P = .07). No interaction was found between onions and CYP1A1*2 for all cell types combined or adenocarcinoma or between this food and other polymorphisms (GSTM1 and CYP2E1) found to be associated with lung cancer in this study (36). Our sample size and the lower consumption of apples and white grapefruit in our population did not allow for similar interaction analyses.

**DISCUSSION**

The flavonol quercetin is quantitatively one of the most important flavo-

---

**Table 2. Odds ratios* (95% confidence intervals) for lung cancer by quantile**

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio (95% confidence interval) by</th>
<th>Two-sided P for trend†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q₁ (low)</td>
<td>Q₂</td>
</tr>
</tbody>
</table>

### A) Intake of flavonoid-rich foods‡

<table>
<thead>
<tr>
<th>Food</th>
<th>Quartile 1 (Referent)</th>
<th>Quartile 2 (0.25–0.50)</th>
<th>Quartile 3 (0.50–0.75)</th>
<th>Quartile 4 (0.75–1)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin</td>
<td>1.0 (Referent)</td>
<td>1.0 (0.9–1.0)</td>
<td>1.0 (0.9–1.0)</td>
<td>0.7 (0.6–0.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Kaempferol</td>
<td>1.0 (Referent)</td>
<td>1.0 (0.9–1.0)</td>
<td>1.0 (0.9–1.0)</td>
<td>0.9 (0.8–1.0)</td>
<td>0.012</td>
</tr>
<tr>
<td>Myricetin</td>
<td>1.0 (Referent)</td>
<td>1.0 (0.9–1.0)</td>
<td>1.0 (0.9–1.0)</td>
<td>0.9 (0.8–1.0)</td>
<td>0.014</td>
</tr>
<tr>
<td>Hesperidin</td>
<td>1.0 (Referent)</td>
<td>1.0 (0.9–1.0)</td>
<td>1.0 (0.9–1.0)</td>
<td>0.9 (0.8–1.0)</td>
<td>0.015</td>
</tr>
<tr>
<td>Naringin</td>
<td>1.0 (Referent)</td>
<td>1.0 (0.9–1.0)</td>
<td>1.0 (0.9–1.0)</td>
<td>0.9 (0.8–1.0)</td>
<td>0.015</td>
</tr>
<tr>
<td>Total flavonoids</td>
<td>1.0 (Referent)</td>
<td>1.0 (0.9–1.0)</td>
<td>1.0 (0.9–1.0)</td>
<td>0.9 (0.8–1.0)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

### B) Flavonoid intakes§

<table>
<thead>
<tr>
<th>Flavonoid</th>
<th>Quartile 1 (Referent)</th>
<th>Quartile 2 (0.25–0.50)</th>
<th>Quartile 3 (0.50–0.75)</th>
<th>Quartile 4 (0.75–1)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin</td>
<td>1.0 (Referent)</td>
<td>1.0 (0.9–1.0)</td>
<td>1.0 (0.9–1.0)</td>
<td>0.7 (0.6–0.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Kaempferol</td>
<td>1.0 (Referent)</td>
<td>1.0 (0.9–1.0)</td>
<td>1.0 (0.9–1.0)</td>
<td>0.9 (0.8–1.0)</td>
<td>0.012</td>
</tr>
<tr>
<td>Myricetin</td>
<td>1.0 (Referent)</td>
<td>1.0 (0.9–1.0)</td>
<td>1.0 (0.9–1.0)</td>
<td>0.9 (0.8–1.0)</td>
<td>0.014</td>
</tr>
<tr>
<td>Hesperidin</td>
<td>1.0 (Referent)</td>
<td>1.0 (0.9–1.0)</td>
<td>1.0 (0.9–1.0)</td>
<td>0.9 (0.8–1.0)</td>
<td>0.015</td>
</tr>
<tr>
<td>Naringin</td>
<td>1.0 (Referent)</td>
<td>1.0 (0.9–1.0)</td>
<td>1.0 (0.9–1.0)</td>
<td>0.9 (0.8–1.0)</td>
<td>0.015</td>
</tr>
<tr>
<td>Total flavonoids</td>
<td>1.0 (Referent)</td>
<td>1.0 (0.9–1.0)</td>
<td>1.0 (0.9–1.0)</td>
<td>0.9 (0.8–1.0)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

*Adjusted by matching for age, sex, and ethnicity and for the following covariates: smoking status, duration, (duration)², number of cigarettes smoked per day, and intakes of β-carotene and saturated fat. These were 582 case–control pairs.

†See “Statistical Methods” section for further details.

‡Tertiles of intake were used for grapefruit, red wine, and white wine. The interquartile ranges (25th–75th percentile) for food intake (g/day) were as follows: onions, 7.5–20.1; broccoli, 5.6–32.0; celery, 2.4–8.0; soy products, 2.0–34.2; apples, 2.3–49.7; other citrus fruits, 18.4–50.0; black tea, 0.0–171.1; and green tea, 0.0–171.1. The intertertile ranges (33rd–67th percentile) for food intake (g/day) were as follows: white grapefruit, 0.0–9.9; pink grapefruit, 0.0–9.9; red wine, 0.0–1.0; and white wine, 0.0–1.0. Soy products include tofu and soybeans eaten alone or in soups and mixed dishes.

§The interquartile ranges (25th–75th percentile) for flavonoid intake (mg/day) were as follows: quercetin, 8.8–16.7; kaempferol, 1.7–5.9; myricetin, 0.4–1.8; and hesperidin, 3.7–38.7. The intertertile range (33rd–67th percentile) for naringin intake (mg/day) was 0.0–2.0.

§Sum of the five flavonoids above. The intertertile range for total flavonoid intake was 23.5–68.9 mg/day.
The flavonoid content of vegetables is known to vary, depending on the food source. For example, the absorption of quercetin from onions is fourfold greater than that from apples or tea (41). The association between onions and squamous cell carcinoma was modified by the CYP1A1 genotype. The lack of a significant association with red wine (another rich source of quercetin) may reflect the low wine consumption of our population. The stronger finding for white grapefruit compared with pink grapefruit may be because naringin is present in pink grapefruit in lesser amounts than in white grapefruit (31). No associations were found with citrus fruits other than grapefruit (sources of hesperidin and tangeretin), black and green teas (which contain flavanols), celery (a good source of luteolin and apigenin), and soy products (an excellent source of isoflavonoids), suggesting that these other flavonoids may not confer the same protection against lung cancer. The findings for white grapefruit may be due to the food composition of this fruit, which contains high amounts of flavonoids (32).

The association between quercetin and white grapefruit was present in almost all ethnic groups and was consistent with the reduction in risk seen for white grapefruit. The inverse associations with onions, apples, and white grapefruit were supported by the finding for onion intake: An inverse association with lung cancer that approached statistical significance was observed for quercetin. Although not statistically significant, the risk estimates for naringin were also consistent with the reduction in risk seen for white grapefruit. The inverse associations with onions, apples, and white grapefruit were present in both sexes and in almost all ethnic groups and were stronger for squamous cell carcinoma. The association between onions and squamous cell carcinoma was modified by the CYP1A1 genotype.

Few past epidemiologic studies have examined the potential protective effect of flavonoids against lung or other cancers. A Dutch cohort study on elderly men (45) found an inverse association between flavonoids and cancers of the respiratory and alimentary tracts, which was limited to fruit and vegetable sources. A larger cohort study of 10 000 Finnish men and women followed for more than 20 years (46) also found a significant inverse association of flavonoid intake with lung cancer.
(of which 95% was quercetin) with lung cancer. The main source of flavonoids (apples) in this Finnish population was
of which 95% was quercetin) with lung cancer and grapefruit. We are not aware of previous reports on lung cancer and grapefruit.

Quercetin has been shown to inhibit carcinogen-induced tumors in rats and mice (18,19). Experimental studies (20) have also shown that quercetin inhibits cytochrome P450 enzymes of the CYP1A1 family. We reasoned that, since CYP1A1 bioactivates polycyclic aromatic hydrocarbons (PAHs) and since a polymorphism in the CYP1A1 gene was associated with squamous cell carcinoma in our data (36), an interaction between onions and this polymorphism would imply that this mechanism could be important in explaining the association with onions. Our finding of such an interaction (albeit of borderline statistical significance) suggests that inhibition of CYP1A1 by quercetin and onions and their effects on PAH activation should be investigated further in humans as a possible protective mechanism against squamous cell carcinoma of the lung. Similarly, naringenin has been shown in laboratory studies to inhibit CYP3A4, an enzyme involved in the metabolism of many xenobiotics, including PAHs (36). In humans, grapefruit juice is well-known to increase the bioavailability of various drugs (e.g., nifedipine and cyclosporine) metabolized by CYP3A4 (48). Thus, CYP3A4 inhibition may be a mechanism by which naringenin and grapefruit could protect against lung cancer.

Among the other flavonoids, flavanols, such as catechins from tea, have been extensively studied in animals. Green tea and black tea have been shown to inhibit lung tumors induced with 4-(methylthio)nitrosamine-1-(3-pyridyl)-1-butane (NNK) in mice (49,50). However, in agreement with our data, past studies reporting on black tea (45,51,52) have found no association with lung cancer. We are not aware of any past studies on green tea and lung cancer. However, Shim et al. (53) reported that the frequency of sister chromatid exchange in mitogen-stimulated peripheral blood lymphocytes from smokers consuming green tea (two to three cups per day) was comparable to that of nonsmokers and significantly lower than that of smokers who did not drink green tea. In the present study, only ethnic Japanese consumed green tea in substantial amounts (average: 124 g/day compared with 12 g/day for Caucasians). Nevertheless, no association was found with lung cancer in this ethnic group (ORs for increasing quartiles: 1.0, 1.0, 0.9, 0.9; P for trend = .76) or in the total sample (Table 2, A).

Experimental studies have suggested that citrus fruit flavonoids may also be protective against lung cancer. Orange and lemon oils included in the diet of mice resulted in a reduction of more than 80% in the yield of NNK-induced lung tumors (54). In contrast, neither citrus fruits (other than grapefruit) nor hesperidin was associated with risk in our data. Koo (55) found an inverse association between soy-product consumption (the main source of isoflavonoids in the diet) and risk of lung cancer among Chinese women who never smoked (OR = 0.3; 95% CI = 0.1–1.1). In this study, we found no association between soy consumption and lung cancer risk, despite soy-consumption levels that are relatively high in ethnic Japanese and Hawaiians in Hawaii (average, 43 g/day and 33 g/day, respectively, in this study).

Much of the interest in the potential chemopreventive effect of flavonoids comes from their antioxidant activity. Flavonoids, like other phenolic antioxidants, eliminate free radicals by donating one electron while remaining chemically unreactive. Since an inverse association was found only for a subset of the flavonoids considered in this study, our data do not suggest a major role for the overall antioxidant effect of flavonoids in lung cancer.

Limitations of this study that need to be considered include possible residual confounding by smoking. We collected detailed information on smoking and gave great care to the way in which we adjusted our analysis for this variable so that residual confounding should have been minimized. To investigate a possible bias from our use of surrogate interviews, we repeated the analyses excluding surrogate respondents. We found very similar results in this subset analysis. In particular, the ORs for increasing quartiles or tertiles of intake were 1.0 (referent), 1.4 (95% CI = 0.8–2.5), 0.9 (95% CI = 0.5–1.6), and 0.4 (95% CI = 0.2–0.8) for onions (P for trend <.001); 1.0 (referent), 0.8 (95% CI = 0.5–1.6), 1.0 (95% CI = 0.5–1.7), and 0.6 (95% CI = 0.3–1.1) for apples (P for trend = .12); and 1.0 (referent), 0.9 (95% CI = 0.4–2.1), and 0.4 (95% CI = 0.2–0.8) for white grapefruit (P for trend = .009). Finally, although interviewed and noninterviewed subjects were similar in their demographics, case patients who were interviewed tended to have a less advanced disease despite our efforts to keep the time short between diagnosis and interview. Thus, the relevance of our findings to particularly fast-growing tumors is unclear. In addition, differences in recall may have occurred between case patients and controls. However, it appears unlikely that such a bias would selectively apply to onions, apples, and grapefruit and not to other sources of flavonoids. Nevertheless, replication of our findings in other settings is desirable, particularly in prospective studies.

In summary, in this case–control study in Hawaii, we found inverse associations between lung cancer and main food sources of quercetin (onions and apples) and naringenin (white grapefruit). Decreased bioactivation of PAHs and other carcinogens by inhibition of CYP1A1 (by quercetin) and CYP3A4 (by naringenin) could be important mechanisms by which these foods may protect against lung cancer.

Journal of the National Cancer Institute, Vol. 92, No. 2, January 19, 2000 REPORTS 159

NOTES

1Editor’s note: SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

Supported in part by Public Health Service grant R01CA55874 and contract N01CP67001 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services; and by grant EDT-78 from the American Cancer Society.

We thank the Hawaii Tumor Registry, Castle Medical Center, Kaiser-Permanente Medical Center, Kuakini Medical Center, Queen’s Medical Center, Straub Clinic and Hospital, St. Francis Medical Center, Tripler Medical Center, and Wahiawa General Hospital for their collaboration. We also thank Ronette Hunt, Barbara Burden, Geraldine Kaneshiro, Carol Lau, and Yun Oh Jung for their technical assistance.

Manuscript received August 20, 1999; revised October 28, 1999; accepted November 15, 1999.