Title
Dietary Flavonoids, Polymorphisms of the Peroxisome Proliferator-Activated Receptors, and Survival of Lung and Upper Aerodigestive Tract Cancers

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Publication Date
2014

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Dietary Flavonoids, Polymorphisms of the Peroxisome Proliferator-Activated Receptors, and Survival of Lung and Upper Aerodigestive Tract Cancers

A thesis submitted in partial satisfaction

of the requirements for the degree

Master of Science in Epidemiology

By

Darlene Veruttipong

2014

ABTRACT OF THESIS

Dietary Flavonoids, Polymorphisms of the Peroxisome Proliferator-Activated Receptors, and Survival of Lung and Upper Aerodigestive Tract Cancers

By

Darlene Veruttipong

Master of Science in Epidemiology

University of California, Los Angeles, 2014

Professor Zuofeng Zhang, Chair

Background: Epidemiologic studies have indicated a protective association between dietary flavonoid intake and lung and upper aerodigestive tract (UADT) cancer risk. Still, the effect of flavonoid intake and lung and UADT cancer survival are unknown. **Methods:** 1,212 (611 lung and 601 UADT) cancer patients were recruited in Los Angeles between 1999-2004 and followed for a median duration of 11 years. Dietary flavonoid intake was ascertained through a food frequency questionnaire (FFQ). Four single nucleotide polymorphisms (SNPs) for peroxisome proliferator-activated receptors (PPARs) : rs3734254, rs10865710, rs1801282, and rs3856806 were gynotyped using Taqman. **Results:** There was no significant association between the subclasses of flavonoids and overall survival. However, there were some significant contrasting associations when stratified by the PPAR SNPs, in which one strata would indicate an increased risk of mortality and the other a decreased risk. Interaction was also detected among lung cancer patients for total flavonoid intake and rs3734254 and rs10865710. Few significant dose response trends were observed. **Conclusion:** Survival may be prolonged or reduced in association to increased flavonoid intake depending on the variant PARR SNPs present among lung and UADT cancer patients.

The thesis of Darlene Veruttipong is approved.

Jianyu Rao

Abdelmonem Afifi

Zuofeng Zhang, Committee Chair

University of California, Los Angeles

2014

TABLE OF CONTENTS

LIST OF TABLES

ACKNOWLEDGEMENTS

This research was partially supported by the National Institutes of Health [Grant Numbers ES011667, CA90833, CA09142, DA11386] and the Alper Research Center for Environmental Genomics of the UCLA Jonsson Comprehensive Cancer Center. The endeavors of this project would not have been possible without the aid of the participants who took the time to contribute to the study as well as the staff who administered the questionnaires, collected the saliva samples, genotyped the DNA, and managed the data files. I would like to thank Dr. Shen-Chih Chang, Andy Lin, and Joni Ricks for providing their expertise.

I would also like to thank classmates, friends, other loved ones, and especially my family: my grandmother Jurai for providing the foundation for me to study, my father for unconditional guidance, and my mother whose wise words still resonate even in her passing.

I am grateful for my advisor Dr. Zuofeng Zhang for is patience, heartfelt advice, and continuous support throughout my years at UCLA and I deeply valued the counsel of the other members of the committee: Dr. Abdelmonem Afifi and Dr. Jianyu Rao.

INTRODUCTION

Lung and upper aerodigestive tract (UADT) cancers are important public health problems globally and in the US. Though there has been a downward trend in lung cancer incidence since the 1980s, worldwide and in the US, lung cancer is the leading diagnosed cancer and cancer-related cause of death [1,2]. Since the 1970s, improvements in surgical techniques and chemoradiation have increased the 1-year survival by about 8.8% [3], yet the 5-year survival rate is still relatively low, 16% in the US[2]. Upper aerodigestive tract cancers, cancers comprise the upper digestive tract and airway, have seen a modest improvement in their survival rates in the US, a 4% increased in the 5-year survival rate in the past decades. The overall 5-year survival rate for cancers that comprise the UADTs cancers in the US are 19%, 65%, and 63% for esophageal , oral cavity and pharynx, and larynx cancer respectively [2].

Flavonoids are a subclass of diverse polyphenols that are ubiquitously found in foods and beverages of plant origin such as fruits, vegetables, teas, and wine. There are greater than 5,000 polyphenolic compounds that can be categorized into six classes: isoflavones, anthocyanidins, flavan-3-ols, flavanones, flavones, and flavonols [4]. The estimated average daily intake of flavonoids of the US population was about 189.7mg/day, where flavan-3-ols made up 82.5% of the intake [5]. Flavonoids have many beneficial activities that help with preventing cancer such as anti-oxidant, anti-inflammatory, and anti-proliferation activities, obstruction of bioactivating enzymes, and the induction of detoxifying enzymes [4]. Previous epidemiologic studies have found that a high intake of flavonoids was associated with a decrease risk of lung or UADT cancers [6–12], while others have found no association[13,14]. Only one study explored the association of flavonoids and survival among cancer patients, specifically breast cancer patients, and found a protective association of certain subclasses of flavonoids and survival [15].

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors of the nuclear hormone receptor superfamily [16]. Three types of PPARs have been identified: PPARα, PPARδ (also called beta), and PPARγ. PPARα is highly expressed in cells that catabolize fatty acids and are a principle regulator of lipid metabolism in the liver[16]. It also regulates inflammation and cell proliferation[17]. PPARδ is necessary for gut and placental development and plays a major role in cell proliferation, differentiation, and survival. Moreover, it is involved in tissue repair and control of cell differentiation, survival, and proliferation[16]. PPARγ has three different isoforms, though there is no known difference between the three. It regulates adipose tissue differentiation, apoptosis, and glucose metabolism[16]. Due to their tumor suppressing behavior, controlling PPAR activity is an appealing approach for treating and preventing cancer. PPARα and PPARγ remain good targets for cancer treatment and prevention, however there are many conflicting studies involving PPARδ and its appropriateness is vague[18].

The relationship between flavonoid intake with lung and UADT cancers risk and the relationship between PPARs and lung cancer risk have been studied. Studies on lung and UADT cancer survival focusing on both flavonoid intake and PPARS are few. The association between dietary flavonoid intake and overall survival among lung and UADT cancer patients has never been elucidated. Examining the associations with flavonoids may help identify food sources that can prolong lung and UADT cancer survival and exploring that relationship in the context of PPARS could help identify subsets of patients who would benefit from increasing their intake of dietary flavonoids.

The objective of this study is to examine the relationship between flavonoids and lung and UADT cancer survival in Los Angeles County from 1994-2004 by secondary analysis of existing data. The specific aims of this study are to examine the relationships of the different subclasses of flavonoids and mortality in lung and UADT cancer patients; to further examine those relationships stratified by PPAR SNPs; and to explore potential interactions between the different flavonoid subclasses and PPAR SNPs.

RESEARCH DESIGN & METHODS

Study Population & Subject Selection

The study population was drawn from the cases of a previous population-based case-control study comprised of 611 newly diagnosed lung cancer cases and 601 new cases of upper aerodigestive tract cancer (oral cancer, pharyngeal cancer, laryngeal cancer and esophageal cancer). The rapid ascertainment system of the Cancer Surveillance Program (CSP) for Los Angeles County was used to histologically confirm the new cases of lung and upper aerodigestive tract cancers (UADT). This system is administered by the University of Southern California (USC) School of Medicine and the USC/Norris Comprehensive Cancer Center. The recruitment period occurred between 1999 and 2004. All of the study subjects had to meet the following criteria: (1) be between 18 to 65 years old; (2) reside in Los Angeles County during the time of diagnosis; and (3) speak English, Spanish, or have a translator available at home. Outliers for a caloric intake 500 calories per a day and > 4500 calories per a day were excluded.

Data Collection and Management

Interviews were conducted in person by specially trained staff using standardized questionnaires and took about 45 to 60 minutes to complete. Self-reported information was collected on socio-demographic characteristics, tobacco smoking history, drug and alcohol use, selected medical history, dietary history, family history of cancer, and other potential protective or risk factors of lung cancer or head and neck cancer.

Afterwards, 25- 50 ml of buccal cells with mouthwash solution were collected in tubes for DNA analysis. All of the samples were transported to the Molecular Epidemiology Laboratory at UCLA, Fielding School of Public Health and stored at – 70°C. The buccal cell samples were separated from the mouthwash by centrifuge and the DNA was separated using a modified phenol-chloroform assay. Single nucleotide polymorphisms (SNPs) that were selected had minor allele frequencies (MAFs) ≥ 5% in Caucasians. The selected SNPs also were non-synonymous or located in regions regulating gene transcriptions, such as promoter areas from the National Center for Biotechnology Information SNP database, when the pairwise linkage disequilibrium (LD) r^2 was ≥ 0.8. A total of one SNP in the gene PPARD (rs3734254) and three SNPs in the gene PPARG (rs10865710, rs1801282, and rs3856806) were selected. Genotyping was carried out without prior knowledge of the study participant's clinical status using Taqman (Applied Biosystems (ABI, Foster City, CA) 7900HT). The thermal cycling conditions were as follows: 10 minutes for 92°C, 60 cycles of denaturing at 92°C for 15 seconds, and annealing at 62°C for 80 seconds. The ABI 7900HT Sequence Detection System was used to read the fluorescence and SDS 2.3 Allelic Discrimination Software was used to genotype each group of alleles.

Death status was verified by linking records to the Social Security Death Index. This analysis focused on all-cause deaths that occurred by October 10, 2014.

<u>Micronutrient and Flavonoid Intake Assessment</u>

A validated food frequency questionnaire (FFQ) adapted from the validated "Brief Block FFQ" (National Cancer Institute) was used to estimate micronutrient and flavonoid intake. Additional fruit and vegetable items were included in the questionnaire for a total of 78 food items. The reference period for the dietary intake was one year before cancer diagnosis, however for seasonal foods during the reference period was limited to the time period in which the food was available. The daily flavonoid intake was calculated by multiplying the portion size (in grams) by the number of servings per a day and its nutrient contents. All of the food items were added together to create the daily nutrient intake for each participant. The portion size of the food items and food composition data were acquired from Dietsys software (version 4.02) and U.S. Department of Agriculture (USDA) portion size database and used to estimate the micronutrient and flavonoid intake.

Statistical Analysis

The flavonoids were grouped into 6 groups: total flavonoids, flavones, flavonols, flavan-3-ols, flavanones, isoflavonoids. Each of the 6 groups was classified into quartiles. The cumulative level of cigarette smoking was measured in pack-years. This was calculated by summing packs/day times the number of years that a subject smoked that amount prior to the diagnosis of cancer. Smoking one pack per day for one year was equal to one pack-year. Wine, beer, and liquor was used to calculate the cumulative level of alcohol drinking by the averaging number of drinks consumed per day. All the SNP genotypes were analyzed using the recessive model.

The cox proportional hazard regression was used to estimate the crude and adjusted hazard ratios (cHRs and aHRs) as well as their 95% confidence intervals (95% CIs). The adjusted hazard ratios were also analyzed stratified by the SNPs. The flavonoid quartiles were treated as ordinal variables and a dose response was tested using p-trend. For the interaction between the flavonoids and the SNPs, the flavonoids dichotomized at the median were used instead of the flavonoid quartiles for ease and meaningfulness of interpretation. For the lung cancer analysis, the adjusted cox proportional hazard models were adjusted using age, sex, education level, race, histology, tumor grade, cumulative cigarette smoking, and calories. For the UADT cancer analysis, the adjusted models adjusted for the same variables as the lung cancer analysis with the addition of the level of alcohol drinking.

The proportional hazard assumption was checked for all models by using the cumulative sums of martingale residuals [19]. Few violations were detected, however non-proportionality did not appear to change the coefficients by more than 0.001% over time and thus an interaction term of the variable with time were not included into the models. The percentage of missing data for each variable was reviewed. It was assumed that the subjects with missing data were a random sample of all the study subjects in the population. Multiple imputation was used to impute the missing values. SAS version 9.2 (SAS Institute Inc., Cary, NC) was used for all analyses.

This study was approved by the institutional review boards of the University of California, Los Angeles and the University of Southern California. Inform consent was obtained from all study participants.

RESULTS

Descriptive Statistics

The distribution of selected demographic variables, potential confounding variables, and the median survival times were summarized in Table 1 by death status and disease status. The average age of diagnoses was slightly higher in those who died than those who were censored in both the lung cancer group, 52.6 years and 51.5 years respectfully, and the UADT, 51.2 years and 49.8 years, respectfully. More than half of the participants were white compared to any other race. The proportion of males to females in the lung cancer study were approximately equal, however there were a greater proportion of males than females in the UADT study, 76% and 24% respectively. The average number of years of education was roughly 13 years.

The median total flavonoid intake was 53.57 mg/day with an interquartile range of 78.09 mg/day. Flavones (median = 15.89 μg/day; interquartile range = 63.24 μg/day), and isoflavonoids (53.32 μg/day; interquartile range = 21.70 μg/day) contributed a small proportion to the total flavonoid intake. Flavonols (median = 5.56 mg/day; interquartile range = 5.18 mg/day), flavanones (median = 18.12 mg/day; interquartile range = 36.50 mg/day), and flavan-3-ols (median = 12.43 mg/day; interquartile range = 34.76 mg/day) contributed to a larger proportion of the total flavonoid intake.

Crude and Adjusted Hazard Ratios

Table 2 presents the crude and adjusted hazard ratios for lung cancer patients. Among lung cancer patients, there was an increase risk of mortality for total flavonoid intake comparing the second quartile to the first quartile in both the crude (cHR = 1.18; 95% CI = 0.88-1.57) and adjusted hazard ratios (aHR = 1.18; 95% CI = 0.88-1.59). Flavonol intake appeared to have a protective association in the adjusted models on all three quartiles, in which the highest quartile of intake compared to the lowest quartile of intake had the greatest protective effect (aHR = 0.82; 95% CI 0.61-1.11). Dose response trends were not observed.

Because there were 141 UADT cases missing flavonoid information, Table 3 presents both with the non-imputed and the imputed values. Using both methods, most of the associations appeared close to null. Flavan-3-ols consistently showed a slight protective association for both the imputed and non-imputed hazard ratios. The flavonone intake showed an inverse association (highest versus lowest quartile non-imputed aHR = 0.71; 95% CI = 0.45-1.11; highest versus lowest quartile imputed aHR = 0.82; 95% CI = 0.55-1.22), however the dose response trend was not significant (non-imputed aHR p-trend = 0.08; imputed aHR p-trend = 0.26).

<u>Stratified Analysis</u>

Tables 4 and 5 present the association of flavonoid intake to mortality stratified by the PPARG and PPARD SNPs in lung cancer patients. Within the TT genotype strata of rs3734254, the total flavonoid intake was associated with an increased risk of death, comparing the highest quartile to the lowest quartile (aHR = 1.73; 95% CI = 1.09-2.74). Conversely, there was an inverse association between total flavonoid intake and mortality for the CT +CC genotype strata (aHR = 0.63; 95% CI = 0.37-1.08). A dose response trend was observed within the strata of the TT genotype (p-trend = 0.03). On all quartiles of flavone intake, there was an inverse association present among the CC genotype stratum of rs10865710 (aHR for second quartile versus lowest quartile = 0.74; 95% CI = 0.48-1.13, aHR for third quartile versus lowest quartile = 0.56; 95% CI = 0.35-0.89, aHR for forth quartile versus lowest quartile = 0.64; 95% CI = 0.41-

1.00). Conversely, there was an increased risk of death on all quartiles within the CG + GG stratum (aHR for second quartile versus lowest quartile =1.61; 95% CI = 1.00-2.61, aHR for third quartile versus lowest quartile = 1.62; 95% CI = 1.00-2.65, aHR for fourth quartile versus lowest quartile = 1.17; 95% CI = 0.69-1.96). The dose response trend was also significant (p-trend = 0.03) for the CC genotype stratum. There was also an inverse association between flavonols and mortality within the CG + GG genotype stratum of rs10865710 comparing the fourth quartile and the first quartile (aHR = 0.52; 95% CI = 0.30-0.89) as well as comparing the third quartile and the first quartile (aHR = 0.49; 95% CI = 0.29-0.82). A dose response trend was observed for the CT + CC stratum (p-trend < 0.01).

Tables 6 through 9 present the association of flavonoid intake to mortality stratified by the PPARG and PPARD SNPs in UADT cancer patients. There was an inverse association between total flavonoid intake greater than 102.80 mg/day and mortality within the CG + GG variant of rs1801282 (highest versus lowest quartile imputed aHR = 0.14; 95% CI = 0.02-0.87, highest versus lowest quartile non-imputed aHR = 0.41; 95% CI = 0.09-1.78). The isoflavonoid intake results also showed a protective association comparing the third quartile to the first quartile (non-imputed aHR = 0.21; 95% CI = 0.05-0.84, imputed aHR = 0.39; 95% CI = 0.10-1.48) as well as the fourth quartile compared to the first quartile (non-imputed aHR = 0.03; 95% CI = 0.00-0.44, imputed aHR = 0.10; 95% CI = 0.01-0.99). The dose response was also significant (p-trend < 0.01). Another isoflavonoid inverse association was present for the fourth quartile compared to the first quartile among those with the CT + TT variant of rs3856806 non-imputed aHR = 0.17; 95% CI = 0.04-0.78, imputed aHR = 0.27; 95% CI = 0.06-1.27). A dose response trend was not observed (non-imputed p-trend = 0.06 and imputed p-trend = 0.09).

Interaction

Table 10 presents the interaction of dichotomized flavonoids and SNPs for lung cancer. The association between total flavonoid intake and mortality differs by rs3734254 and rs10865710 variants, aHR = 0.59; 95% CI = 0.37-0.96 and aHR = 0.58; 95% CI = 0.37- 0.92, respectively. The association between flavonols and mortality differs by rs3734254 variants, aHR = 0.53; 95% CI = 0.33-0.84). The association between flavanone intake and mortality differs by rs10865710 variants, aHR = 0.63; 95% CI = 0.40-1.00.

Table 11 and 12 presents the interaction of dichotomized flavonoids and SNPs for UADT cancer. The association between flavonols and mortality differs by rs1801282, aHR = 0.36; 95% CI = 0.14-0.97. However this finding was not present with the imputed data (aHR = 0.74; 95% CI = 0.31-1.77). The association between isoflavonoids differed by both rs1801282 and rs3856806 variants, aHR = 0.38; 95% CI = 0.15-0.97 and aHR = 0.35; 95% CI = 0.15-0.83 respectively. Though the interaction was absent in the imputed results (rs1801282 aHR = 0.67; 95% CI = 0.28-1.56, rs3856806 aHR = 0.58; 95% CI = 0.27-1.26).

DISCUSSION

To our knowledge, this is the first study to investigate the flavonoid intake on lung and UADT cancer survival in a diverse US population. Lung cancer cases also showed a modest protective effect for the association of flavones and mortality as well as the association of flavonols and mortality, though the results were not significant. Among the UADT cancer cases, flavan-3-ols appeared to have a modest decrease risk of death on all three quartiles. Dose response trends were not observed. When the results were stratified by the PPAR SNPs, the risk of mortality was more disparate for some of the associations, in which one variant of a SNP would show an increase risk of mortality and other variant showing a decreased risk. When looking at the interaction of the dichotomized flavonoids and SNPs, we found that among the lung cancer cases the association of total flavonoid intake and mortality was modified by rs3734254 and rs10865710. For UADT, the rs1801282 and rs3856806 modified the association of flavonols and mortality as well as isoflavonoids and mortality. There was no evidence of interaction in the imputed versions of these models.

The results of the study could provide a provisional suggestion of the relationship between lung cancer survival and dietary flavonoid intake. Previous studies of flavonoid intake and lung cancer have shown inconsistent findings. The results of this study are consistent with the previous etiological studies that did not support the major role of flavonoids in lung cancer prevention[13,14]. Increased flavonoid intake, which had demonstrated a decrease risk of lung cancer in previous studies, did not consistently show a decrease risk for mortality for all 5 types of flavonoids for this study. Similarly, the results for the UADT cancers did not reflect the protective association of the flavonoids seen in previous studies [10,11,20]. There could be several reasons for the nearly null findings in this study. One reason could be a relatively low range of intake. This was a multiethnic study and people in non-Caucasian ethnic groups may have consumed flavonoids that were not ascertained in the FFQ. The studies that were done in Europe have largely a homogenous population with a homogenous diet. Their food frequency questionnaires could have been modified to more accurately capture their diet. Though the sample size was relatively large in this study, the number of cases in each quartile may not have been large enough to detect an association. The studies that have shown a decrease risk of lung cancer risk had very large sample sizes [7,9] .

We also saw different associations of flavonoid with mortality when stratified by the SNPs. There was also evidence of interaction. The mechanisms for which flavonoids and PPARs act and their relationship to cancer are just recently being elucidated. An in vitro study showed that PPARγ plays a pivotal role in the antiproliferative effects of quercetin metabolites, metabolites of a flavonol [21]. Quercetin metabolites significantly increased the expression of PPARγ and PTEN. Levels of phospho-Akt in A549 cells also decreased in a dose-dependent manner. There is evidence that indicates that the activation of PTEN and the suppression of Akt play are crucial for the antiproliferative effect of PPAR-γ in lung cancer cells [21] . Two in vitro studies investigated how hesperidin, the most common flavonoid found in citrus fruit, inhibited cancer cell proliferation and induced apoptosis through a PPARγ dependent mechanism. One of the studies demonstrated that hesperidin induces the expression and transcriptional activity in PPARγ. The activation of PPARγ subsequently promotes the expression of the tumor suppressor p53[22] and in part inhibits the activation of NF- κB, whose transcription factors can prevent apoptosis[22,23].

There were very few statistically significant dose response trends observed in the results. This could suggest that a wider range of flavonoid intake, a larger sample size, or an increased data collection on foods rich in flavonoids is necessary to detect a dose response. It could also be possible that rather than a dose response effect, there is a threshold effect. Most of the significant findings were mainly those comparing the highest quartile to the lowest quartile.

<u>Strengths & Limitations</u>

This is the first study to look at lung and UADT cancers and survival. The strengths of this study are that it has a relatively large sample size, mirroring the diverse population of Los Angeles County. Also, a comprehensive questionnaire was used to collect detailed information on known risk factors such as diet, drinking, cigarette smoking. Despite these strengths, there are several limitations.

There may be me some error in measuring the micronutrients due to the innate limitations of the food frequency questionnaire (FFQ). Measurement error could also occur from retrospectively collecting the data. The collected data from the FFQ may not reflect dietary exposure before lung cancer diagnosis. Cases may try to over report their fruit and vegetable intake or underreport their smoking and drinking habits. Selection bias could occur. Lung and UADT patients who have a poor prognosis or rapid progression may prevent them from participating in the study, though this exclusion has been minimized by identifying cases shortly after their diagnosis through active surveillance. There may be residual confounding, despite controlling for well documented risk factors. There are thousands of flavonoids and other biologically active compounds. It is possible that these molecules could be correlated with the flavonoids used in the study. There should be minimal bias in regards to the SNPS because the polymorphisms should be predetermined. However, the genotyping results could be affected because the buccal swab samples of the cancer patients may contain normal cells. Lastly, information on TNM (tumor node metastasis) staging was not collected for the study. Instead, tumor differentiation grade was used in its place. Tumor grade is not an exact proxy for TNM staging and could result in misclassification.

Public Health Implications & Future Directions

The results of this study may have some implications on the treatment or diet after cancer diagnosis. It suggested that people with certain genotypes may benefit from increasing flavonoid intake, while others may be harmed. In other words, survival may be prolonged or reduced in association to increased flavonoid intake depending on the variant PARR SNPs present among lung and UADT cancer patients. This information can be further used for dietary recommendations, public health intervention studies, or to help identify subsets of cancer patients who could benefit from increasing flavonoid intake. Future studies should use a questionnaire that focuses on lung and UADT and the joint effects of flavonoid intake and the PPAR SNPs.

APPENDICES

Table 1. Demographic Characteristics of Lung and UADT Cancers

	Lung Cancer (N=611)				UADT (N=601)			
	All, n	Death, n (%)	Censored, n (%)	Median Survival Years	All, n	Death, n (%)	Censored, n (%)	Median Survival Years
Total	611	406 (66)	205 (34)	2.5	601	248 (41)	353 (59)	9.4
Age (Years)								
<45	61	38 (62)	23 (38)	3.0	109	38 (35)	71 (65)	10.1
45-54	301	188 (62)	113 (38)	2.9	267	105 (39)	162 (61)	9.6
55+	249	180 (72)	113 (38)	2.2	225	105 (47)	120 (53)	9.0
Sex								
Male	303	215 (71)	88 (29)	2.0	454	191 (42)	263 (58)	9.3
Female	308	191 (62)	117 (38)	3.7	147	57 (39)	90 (61)	9.7
Ethnicity								
Caucasian	359	245 (68)	114 (32)	2.4	341	135 (40)	206 (60)	9.4
Hispanic	70	44 (63)	26 (37)	2.2	109	46 (42)	63 (58)	9.4
African-American	96	60 (62)	36 (38)	3.0	69	39 (56)	30 (43)	5.6
Asian-American	70	46 (66)	24 (34)	2.8	64	21 (33)	43 (67)	9.9
Other	15	10 (67)	5 (33)	4.1	16	6 (38)	10 (62)	9.0
Education								
0-12 Years	265	181 (68)	84 (32)	2.6	273	117 (43)	156 (57)	9.3
13-16 Years	275	181 (66)	94 (34)	2.4	259	110 (42)	149 (58)	9.4
≥ 17 Years	71	44 (62)	27 (38)	2.8	69	21 (30)	48 (70)	10.1
Histology								
Squamous Cell Carcinoma	95	53 (56)	42 (44)	5.8	497	195 (39)	302 (61)	9.6
Adenocarcinoma	297	186 (63)	111 (34)	3.4	74	42 (57)	32 (43)	3.6
Large Cell Carcinoma	115	85 (74)	30 (26)	2.1	-	-	-	-
Small Cell Carcinoma	75	60 (80)	15 (20)	1.4	-	-	-	-
Other	29	22 (76)	7 (24)	1.5	30	11 (37)	19 (63)	9.9
Tumor Grade								
Well to moderate	169	90 (53)	79 (47)	7.2	399	172 (43)	227 (57)	9.3
Poor to very poor	222	154 (69)	68 (31)	2.0	121	42 (35)	79 (65)	9.8
Undetermined	219	161 (74)	58 (26)	2.0	81	34 (42)	47 (58)	9.6
Smoking (Pack-Years)								
0	110	61 (55)	49 (44)	5.5	182	53 (29)	129 (71)	10.1
< 20	98	63 (64)	35 (36)	2.6	145	51 (35)	94 (65)	9.7
20 to 40	201	139 (69)	62 (31)	2.5	146	71 (49)	75 (51)	8.8
40+	202	143 (71)	59 (29)	1.9	128	73 (57)	55 (43)	6.8
Drinking Status (Drink-day)								
0	170	111 (65)	59 (34)	2.8	117	45 (38)	72 (62)	9.8
< 2	302	200 (66)	102 (34)	2.4	279	97 (35)	182 (65)	9.8

≥ 2	138	94 (68)	44 (32)	2.8	203	105 (52)	98 (48)	8.2

Table 2. Crude and Adjusted Hazard Ratios of Flavonoid Intake and Overall Survival Among Lung Cancers

Flavonoid Intake (mg/day)	Death/All	cHR (95% CI)	aHR* (95% CI)
Total Flavonoid			
0 – 24.71	90/140	1.00	1.00
24.71– 53.57	95/139	1.18 (0.88-1.57)	1.18 (0.88-1.59)
53.57– 102.80	95/140	1.10 (0.83-1.47)	1.03 (0.77-1.37)
102.80+	95/139	1.13 (0.85-1.49)	1.06 (0.79-1.43)
P_{trend}		0.48	0.88
Flavones			
0 - 0.0025	106/147	1.00	1.00
0.0025 – 0.016	78/109	0.92 (0.70-1.22)	1.00 (0.75-1.33)
0.016 – 0.066	96/156	0.89 (0.67-1.18)	0.89 (0.67-1.19)
0.066 +	95/146	0.88 (0.66-1.17)	0.87 (0.65-1.16)
P_{trend}		0.36	0.27
Flavonols			
0 – 3.28	96/140	1.00	1.00
3.28– 5.56	93/139	0.95 (0.72-1.25)	0.90 (0.68-1.20)
5.56– 8.46	96/140	1.00 (0.75-1.32)	0.89 (0.66-1.19)
8.46+	90/139	0.96 (0.72-1.27)	0.82 (0.61-1.11)
P_{trend}		0.84	0.21
Flavan-3-ols			
0 – 4.00	93/139	1.00	1.00
4.00– 12.43	85/140	0.95 (0.71-1.27)	0.92 (0.68-1.23)
12.43– 38.75	97/139	1.11 (0.83-1.48)	1.08 (0.80-1.46)
38.75+	100/140	1.13 (0.86-1.50)	1.06 (0.79-1.41)
P_{trend}		0.24	0.49
Flavanones			
0 – 4.18	98/142	1.00	1.00
4.18– 18.12	92/145	0.89 (0.67-1.18)	0.93 (0.69-1.24)
18.12– 40.68	92/132	0.97 (0.73-1.30)	1.04 (0.77-1.41)
40.68+	93/139	0.96 (0.73-1.28)	0.94 (0.70-1.27)
P_{trend}		0.97	0.89
Isoflavonoids			
0 – 0.017	97/147	1.00	1.00
0.017– 0.053	88/132	1.05 (0.80-1.38)	0.93 (0.70-1.24)
0.053– 0.23	98/137	1.19 (0.90-1.57)	1.05 (0.78-1.41)
0.23+	92/142	0.93 (0.69-1.26)	0.92 (0.65-1.30)
P_{trend}		1.00	0.90

* Adjusted by age, sex, race/ethnicity, education level, histology, tumor grade, calories, packyears

Table 3. Crude and Adjusted Hazard Ratios of Flavonoid Intake and Overall Survival Among UADT Cancers

Flavonoid Intake (mg/day)	Non-Imputed Hazard Ratios			Imputed Hazard Ratios	
	Death/All	cHR (95% CI)	aHR* (95% CI)	cHR (95% CI)	aHR* (95% CI)
Total Flavonoid					
0 – 24.71	34/83	1.00	1.00	1.00	1.00
24.71– 53.57	59/132	1.08 (0.72-1.61)	1.10 (0.73-1.66)	1.07 (0.72-1.59)	1.06 (0.71-1.59)
53.57– 102.80	46/120	0.83 (0.54-1.27)	0.80 (0.52-1.25)	0.84 (0.56-1.26)	0.88 (0.58-1.33)
102.80+	44/110	0.91 (0.60-1.40)	0.95 (0.61-1.48)	0.91 (0.62-1.33)	0.95 (0.64-1.42)
P_{trend}		0.40	0.49	0.37	0.60
Flavones					
0 - 0.0025	53/115	1.00	1.00	1.00	1.00
0.0025 – 0.016	29/76	0.92 (0.62-1.39)	1.06 (0.70-1.60)	0.97 (0.66-1.44)	1.11 (0.75-1.64)
0.016 – 0.066	58/130	0.91 (0.61-1.36)	0.94 (0.62-1.43)	0.94 (0.64-1.36)	1.05 (0.71-1.56)
0.066 +	43/124	0.85 (0.56-1.29)	0.97 (0.63-1.50)	0.85 (0.57-1.25)	0.97 (0.64-1.46)
P_{trend}		0.45	0.75	0.39	0.85
Flavonols					
0 – 3.28	30/79	1.00	1.00	1.00	1.00
3.28– 5.56	49/109	1.13 (0.74-1.72)	1.14 (0.73-1.77)	1.03 (0.69-1.54)	1.07 (0.71-1.60)
5.56– 8.46	53/130	0.90 (0.59-1.38)	0.88 (0.55-1.39)	0.84 (0.57-1.25)	0.86 (0.57-1.30)
8.46+	51/127	1.02 (0.67-1.56)	0.96 (0.60-1.51)	0.94 (0.64-1.38)	0.91 (0.60-1.36)
P_{trend}		0.77	0.54	0.54	0.43
Flavan-3-ols					
0 – 4.00	44/97	1.00	1.00	1.00	1.00
4.00– 12.43	48/113	0.87 (0.58-1.31)	0.92 (0.60-1.39)	0.90 (0.62-1.31)	0.96 (0.65-1.43)
12.43– 38.75	54/141	0.84 (0.56-1.25)	0.80 (0.52-1.21)	0.85 (0.58-1.24)	0.84 (0.56-1.26)
38.75+	37/94	0.76 (0.50-1.17)	0.81 (0.52-1.26)	0.83 (0.57-1.20)	0.85 (0.58-1.25)
P_{trend}		0.21	0.27	0.30	0.33
Flavanones					
0 – 4.18	50/108	1.00	1.00	1.00	1.00
4.18– 18.12	49/107	0.97 (0.65-1.44)	1.04 (0.69-1.58)	0.98 (0.66-1.43)	1.03 (0.67-1.54)
18.12– 40.68	48/134	0.76 (0.51-1.14)	0.81 (0.53-1.22)	0.81 (0.55-1.20)	0.92 (0.62-1.37)
40.68+	36/96	0.74 (0.49-1.13)	0.71 (0.45-1.11)	0.75 (0.52-1.09)	0.82 (0.55-1.22)
P_{trend}		0.09	0.08	0.09	0.26
Isoflavonoids					
0 – 0.017	36/88	1.00	1.00	1.00	1.00
0.017– 0.053	28/71	1.05 (0.66-1.66)	1.01 (0.63-1.62)	0.98 (0.65-1.47)	1.02 (0.67-1.55)
0.053– 0.23	57/115	1.14 (0.76-1.69)	1.09 (0.71-1.67)	0.97 (0.67-1.40)	0.99 (0.68-1.46)
0.23+	62/171	0.80 (0.52-1.22)	1.07 (0.67-1.73)	0.70 (0.47-1.04)	0.93 (0.60-1.43)
P_{trend}		0.36	0.69	0.09	0.75

* Adjusted by age, sex, race/ethnicity, education level, histology, tumor grade, calories, packyears, drinkday

Table 4. Adjusted Hazard Ratios of Flavonoid Intake and Overall Survival Among Lung Cancers, Stratified by rs3734254 and rs10865710

Flavonoid Intake (mg/day)	rs3734254 (N = 467)			rs10865710 (N = 472)		
	Death/All	TT aHR* (95% CI)	CT + CC aHR* (95% CI)	Death/All	CC aHR* (95% CI)	CG + GG aHR* (95% CI)
Total Flavonoid						
0 – 24.71	71/115	1.00	1.00	68/114	1.00	1.00
24.71– 53.57	81/121	1.56 (0.98-2.50)	1.10 (0.68-1.77)	80/118	1.44 (0.88-2.37)	1.32 (0.82-2.12)
53.57– 102.80	82/119	1.45 (0.93-2.25)	0.86 (0.52-1.45)	88/127	1.48 (0.94-2.33)	0.85 (0.52-1.38)
102.80+	74/112	***1.73 (1.09-2.74)***	0.63 (0.37-1.08)	78/113	1.57 (0.99-2.49)	0.98 (0.58-1.64)
P_{trend}		***0.03***	0.07		0.06	0.51
Flavones						
0 - 0.0025	85/119	1.00	1.00	85/119	1.00	1.00
0.0025 – 0.016	68/96	1.13 (0.74-1.71)	0.72 (0.43-1.22)	69/96	0.74 (0.48-1.13)	***1.61 (1.00-2.61)***
0.016 – 0.066	80/131	0.90 (0.59-1.39)	0.93 (0.56-1.54)	81/132	***0.56 (0.35-0.89)***	***1.62 (1.00-2.65)***
0.066 +	75/121	0.86 (0.54-1.36)	0.74 (0.45-1.21)	79/125	***0.64 (0.41-1.00)***	1.17 (0.69-1.96)
P_{trend}		0.37	0.36		0.03	0.45
Flavonols						
0 – 3.28	78/115	1.00	1.00	77/116	1.00	1.00
3.28– 5.56	79/119	1.14 (0.74-1.76)	0.85 (0.53-1.37)	78/113	1.41 (0.89-2.22)	0.83 (0.52-1.33)
5.56– 8.46	78/115	1.13 (0.73-1.76)	***0.57 (0.34-0.97)***	84/122	0.97 (0.59-1.58)	0.91 (0.58-1.45)
8.46+	73/118	1.19 (0.76-1.89)	***0.49 (0.29-0.82)***	75/121	1.09 (0.68-1.73)	***0.52 (0.30-0.89)***
P_{trend}		0.47	**0.00**		0.80	***0.04***
Flavan-3-ols						
0 – 4.00	76/114	1.00	1.00	77/119	1.00	1.00
4.00– 12.43	74/123	0.88 (0.57-1.36)	0.96 (0.58-1.59)	72/116	0.87 (0.53-1.43)	1.09 (0.67-1.79)
12.43– 38.75	78/118	1.06 (0.65-1.71)	1.02 (0.67-1.67)	83/122	1.23 (0.77-1.96)	1.11 (0.68-1.83)
38.75+	80/112	1.39 (0.91-2.14)	0.68 (0.40-1.17)	82/115	1.30 (0.83-2.04)	0.85 (0.50-1.43)
P_{trend}		0.08	0.22		0.1047	0.5908
Flavanones						
0 – 4.18	82/122	1.00	1.00	79/120	1.00	1.00
4.18– 18.12	73/118	1.17 (0.76-1.81)	0.61 (0.36-1.01)	73120	0.98 (0.61-1.56)	0.99 (0.60-1.63)
18.12– 40.68	78/112	1.14 (0.71-1.82)	1.10 (0.66-1.83)	79/111	1.29 (0.79-2.12)	1.12 (0.69-1.82)
40.68+	75/115	1.25 (0.81-1.93)	0.68 (0.39-1.19)	83/121	1.43 (0.92-2.24)	0.84 (0.50-1.40)
P_{trend}		0.3515	0.56		0.0601	0.6541
Isoflavonoids						
0 – 0.017	76/121	1.00	1.00	73/118	1.00	1.00
0.017– 0.053	75/112	1.33 (0.86-2.05)	0.66 (0.39-1.11)	77/114	0.94 (0.60-1.49)	1.25 (0.77-2.05)
0.053– 0.23	79/113	1.49 (0.95- 2.34)	0.77 (0.46-1.29)	85/119	1.15 (0.75-1.76)	1.40 (0.83-2.36)

0.23+	78/121	1.31 (0.75-2.28)	0.61 (0.34-1.11)	79/121	1.30 (0.76-2.20)	0.77 (0.42-1.39)
P_{trend}		0.18	0.13		0.2686	0.6741

* Adjusted by age, sex, race/ethnicity, education level, histology, tumor grade, calories, packyears

Table 5. Adjusted Hazard Ratios of Flavonoid Intake and Overall Survival Among Lung Cancers, Stratified by rs1801282 and rs3856806

	rs1801282 (N = 489)			rs3856806 (N = 498)		
Flavonoid Intake (mg/day)	Death/All	CC aHR* (95% CI)	CG + GG aHR* (95% CI)	Death/All	CC aHR* (95% CI)	CT + TT aHR* (95% CI)
Total Flavonoid						
0 – 24.71	73/120	1.00	1.00	75/122	1.00	1.00
24.71– 53.57	83/123	1.43 (1.00-2.05)	1.66 (0.66-4.19)	85/125	1.32 (0.91-1.91)	1.48 (0.71-3.07)
53.57– 102.80	89/128	1.21 (0.85-1.71)	1.58 (0.62-4.01)	89/129	1.10 (0.77-1.57)	1.12 (0.52-2.43)
102.80+	80/118	1.24 (0.86-1.78)	0.96 (0.35-2.67)	83/122	1.23 (0.84-1.78)	1.00 (0.49-2.01)
P_{trend}		0.38	0.89		0.40	0.90
Flavones						
0 - 0.0025	92/128	1.00	1.00	94/130	1.00	1.00
0.0025 – 0.016	71/99	0.96 (0.69-1.35)	2.33 (0.90-6.01)	72/100	0.94 (0.66-1.32)	1.49 (0.73-3.01)
0.016 – 0.066	84/138	0.80 (0.57-1.12)	1.95 (0.74-5.11)	85/139	0.82 (0.58-1.16)	1.49 (0.70-3.14)
0.066 +	78/124	0.75 (0.53-1.06)	***7.07 (2.20-22.75)***	81/129	***0.70 (0.48-1.00)***	1.87 (0.92-3.81)
P_{trend}		0.05	***0.00***		***0.04***	0.09
Flavonols						
0 – 3.28	78/118	1.00	1.00	82/122	1.00	1.00
3.28– 5.56	83/124	1.01 (0.71-1.42)	2.00 (0.86-4.62)	83/124	1.02 (0.72-1.44)	0.97 (0.49-1.91)
5.56– 8.46	86/125	0.97 (0.68-1.38)	0.92 (0.36-2.35)	87/126	0.98 (0.68-1.42)	0.92 (0.46-1.86)
8.46+	78/122	0.90 (0.63-1.28)	0.74 (0.26-2.08)	80/126	0.83 (0.58-1.20)	0.59 (0.27-1.31)
P_{trend}		0.51	0.53		0.33	0.24
Flavan-3-ols						
0 – 4.00	81/123	1.00	1.00	83/125	1.00	1.00
4.00– 12.43	75/124	0.94 (0.66-1.34)	0.70 (0.25-1.95)	76/125	0.95 (0.66-1.37)	1.01 (0.51-1.99)
12.43– 38.75	84/123	1.14 (0.80-1.63)	1.29 (0.54-3.07)	86/126	1.23 (0.85-1.78)	0.77 (0.37-1.60)
38.75+	85/119	1.07 (0.76-1.51)	0.80 (0.34-1.89)	87/122	1.19 (0.84-1.70)	0.66 (0.33-1.31)
P_{trend}		0.50	0.86		0.19	0.20
Flavanones						
0 – 4.18	82/124	1.00	1.00	85/127	1.00	1.00
4.18– 18.12	77/125	0.95 (0.66-1.36)	0.87 (0.60-1.26)	77/126	0.87 (0.60-1.26)	1.32 (0.63-2.75)
18.12– 40.68	83/117	1.35 (0.95-1.92)	1.14 (0.79-1.64)	84/118	1.14 (0.79-1.64)	1.65 (0.77-3.54)
40.68+	83/123	1.08 (0.76-1.53)	1.08 (0.76-1.56)	86/127	1.08 (0.76-1.56)	0.97 (0.41-2.29)
P_{trend}		0.34	0.28		0.41	0.74
Isoflavonoids						
0 – 0.017	79/126	1.00	1.00	81/129	1.00	1.00
0.017– 0.053	80/117	0.96 (0.69-1.36)	2.32 (0.87-6.16)	82/120	1.02 (0.72-1.44)	1.05 (0.51-2.17)
0.053– 0.23	83/118	1.06 (0.75-1.50)	2.85 (0.92-8.81)	86/121	1.19 (0.84-1.70)	0.82 (0.39,1.74)
0.23+	83/128	0.84 (0.56-1.27)	1.87 (0.52-6.78)	83/128	0.93 (0.60-1.44)	1.15 (0.46-2.85)

P_{trend}	0.66	0.26		0.80	0.88

* Adjusted by age, sex, race/ethnicity, education level, histology, tumor grade, calories, packyears

Table 6. Adjusted Hazard Ratios of Flavonoid Intake and Overall Survival Among UADT Cancers, Stratified by rs3734254

Flavonoid Intake (mg/day)	Death/All	Non-Imputed Hazard Ratios TT aHR* (95% CI)	Non-Imputed Hazard Ratios CT + CC aHR* (95% CI)	Imputed Hazard Ratios TT aHR* (95% CI)	Imputed Hazard Ratios CT + CC aHR* (95% CI)
Total Flavonoid					
0 – 24.71	27/61	1.00	1.00	1.00	1.00
24.71– 53.57	48/109	1.64 (0.89-3.02)	0.56 (0.26-1.22)	1.55 (0.83-2.88)	0.55 (0.26-1.15)
53.57– 102.80	32/83	0.96 (0.49-1.89)	0.63 (0.26-1.51)	1.04 (0.55-1.97)	0.70 (0.32-1.56)
102.80+	29 /81	1.20 (0.63-2.26)	0.33 (0.11-1.02)	1.15 (0.64-2.07)	0.53 (0.22-1.29)
P_{trend}		0.99	0.07	0.96	0.25
Flavones					
0 - 0.0025	39/80	1.00	1.00	1.00	1.00
0.0025 – 0.016	22/54	0.86 (0.48-1.54)	1.20 (0.39-3.64)	0.96 (0.55-1.66)	1.33 (0.51-3.49)
0.016 – 0.066	43/105	0.54 (0.28-1.02)	1.43 (0.57-3.60)	0.74 (0.40-1.36)	1.32 (0.52-3.32)
0.066 +	32/95	0.73 (0.38-1.42)	1.61 (0.62-4.22)	0.83 (0.43-1.61)	1.19 (0.50-2.84)
P_{trend}		0.14	0.29	0.41	0.74
Flavonols					
0 – 3.28	19/55	1.00	1.00	1.00	1.00
3.28– 5.56	42/87	1.10 (0.57-2.15)	1.80 (0.75-4.29)	1.01 (0.55-1.87)	1.40 (0.62-3.14)
5.56– 8.46	42/100	0.88 (0.46-1.74)	0.76 (0.28-2.11)	0.88 (0.47-1.63)	0.75 (0.28-2.00)
8.46+	33/92	0.88 (0.44-1.75)	0.65 (0.21-2.05)	0.88 (0.47-1.62)	0.71 (0.27-1.92)
P_{trend}		0.53	0.17	0.56	0.25
Flavan-3-ols					
0 – 4.00	32/69	1.00	1.00	1.00	1.00
4.00– 12.43	41/92	0.92 (0.49-1.74)	0.91 (0.41-2.01)	1.05 (0.58-1.87)	0.94 (0.45-2.00)
12.43– 38.75	42/112	0.83 (0.42-1.62)	0.62 (0.26-1.48)	0.96 (0.50-1.81)	0.64 (0.28-1.44)
38.75+	21/61	0.75 (0.38-1.48)	0.50 (0.15-1.60)	0.85 (0.46-1.57)	0.65 (0.25-1.69)
P_{trend}		0.37	0.15	0.53	0.25
Flavanones					
0 – 4.18	38/78	1.00	1.00	1.00	1.00
4.18– 18.12	35/78	0.88 (0.48-1.63)	1.28 (0.51-3.18)	1.09 (0.59-2.01)	1.28 (0.55-2.93)
18.12– 40.68	34/98	0.76 (0.40-1.45)	0.88 (0.36-2.15)	1.03 (0.57-1.89)	0.97 (0.43-2.18)
40.68+	29/80	0.82 (0.44-1.52)	0.61 (0.23-1.63)	0.93 (0.52-1.67)	0.88 (0.36-2.13)
P_{trend}		0.46	0.24	0.77	0.63
Isoflavonoids					
0 – 0.017	23/65	1.00	1.00	1.00	1.00
0.017– 0.053	19/52	0.62 (0.30-1.30)	***3.13 (1.17-8.34)***	0.69 (0.36-1.32)	2.04 (0.82-5.09)
0.053– 0.23	47/93	1.23 (0.68-2.23)	1.03 (0.39-2.75)	0.95 (0.54-1.68)	1.06 (0.46-2.44)
0.23+	47/124	1.07 (0.52-2.19)	1.81 (0.66-4.98)	0.88 (0.45-1.71)	1.46 (0.57-3.73)

P_{trend}	0.40	0.67	1.00	0.74

* Adjusted by age, sex, race/ethnicity, education level, histology, tumor grade, calories, packyears, drinkday

Table 7. Adjusted Hazard Ratios of Flavonoid Intake and Overall Survival Among UADT Cancers, Stratified by rs10865710

Flavonoid Intake (mg/day)	Death/All	Non-Imputed Hazard Ratios CC aHR* (95% CI)	Non-Imputed Hazard Ratios CG + GG aHR* (95% CI)	Imputed Hazard Ratios CC aHR* (95% CI)	Imputed Hazard Ratios CG + GG aHR* (95% CI)
Total Flavonoid					
0 – 24.71	25/62	1.00	1.00	1.00	1.00
24.71– 53.57	48/108	0.98 (0.49-1.98)	1.66 (0.82-3.35)	0.84 (0.43-1.63)	1.49 (0.76- 2.93)
53.57– 102.80	33/84	0.71 (0.33-1.53)	0.85 (0.40-1.77)	0.79 (0.40-1.56)	0.95 (0.46-1.96)
102.80+	27/74	0.65 (0.29-1.48)	0.95 (0.45-2.00)	0.74 (0.37-1.48)	1.06 (0.51-2.21)
P_{trend}		0.19	0.68	0.03	0.89
Flavones					
0 - 0.0025	38/82	1.00	1.00	1.00	1.00
0.0025 – 0.016	20/52	0.75 (0.36-1.57)	1.25 (0.62-2.54)	0.95 (0.50-1.83)	1.11 (0.56-2.20)
0.016 – 0.066	44/103	0.60 (0.28-1.26)	1.13 (0.57-2.25)	0.77 (0.39-1.54)	1.13 (0.58- 2.19)
0.066 +	31/91	1.00 (0.50-2.01)	0.96 (0.41-2.23)	1.00 (0.50-2.00)	0.80 (0.37-1.74)
P_{trend}		0.83	0.97	0.85	0.72
Flavonols					
0 – 3.28	20/58	1.00	1.00	1.00	1.00
3.28– 5.56	38/ 83	1.62 (0.76-3.45)	0.88 (0.42-1.88)	1.37 (0.70-2.68)	0.81 (0.38-1.74)
5.56– 8.46	43/101	1.15 (0.53-2.48)	0.53 (0.23-1.21)	1.22 (0.61-2.44)	0.57 (0.24-1.31)
8.46+	32/86	0.70 (0.29-1.70)	0.79 (0.36-1.76)	0.85 (0.39-1.89)	0.81 (0.38- 1.75)
P_{trend}		0.30	0.39	0.57	0.51
Flavan-3-ols					
0 – 4.00	31/70	1.00	1.00	1.00	1.00
4.00– 12.43	39/92	0.82 (0.41-1.63)	1.04 (0.51-2.12)	0.85 (0.44-1.65)	1.11 (0.53-2.31)
12.43– 38.75	43/110	0.86 (0.44-1.68)	1.14 (0.54-2.40)	0.88 (0.45-1.74)	1.14 (0.53-2.46)
38.75+	20/56	0.51 (0.22-1.18)	0.95 (0.42-2.17)	0.65 (0.32-1.29)	1.18 (0.53-2.60)
P_{trend}		0.17	1.00	0.25	0.70
Flavanones					
0 – 4.18	36/77	1.00	1.00	1.00	1.00
4.18– 18.12	33/76	0.59 (0.27-1.26)	1.13 (0.53-2.40)	0.83 (0.39-1.76)	1.21 (0.59-2.49)
18.12– 40.68	36/99	0.82 (0.40-1.67)	0.73 (0.35-1.54)	1.02 (0.51-2.03)	0.82 (0.39-1.73)
40.68+	28/76	0.47 (0.21-1.06)	0.68 (0.32-1.47)	0.80 (0.38-1.69)	0.76 (0.36-1.59)
P_{trend}		0.16	0.18	0.72	0.29
Isoflavonoids					
0 – 0.017	23/65	1.00	1.00	1.00	1.00
0.017– 0.053	20/ 53	1.43 (0.54-3.78)	1.01 (0.47-2.20)	1.30 (0.60-2.80)	0.93 (0.45-1.89)
0.053– 0.23	46/91	1.22 (0.54-2.77)	1.13 (0.56-2.29)	1.24 (0.62-2.48)	1.01 (0.51-1.99)
0.23+	44/119	***2.47 (1.08-5.65)***	0.70 (0.29-1.65)	1.62 (0.78-3.35)	0.63 (0.27-1.49)

P_{trend}	0.06	0.63	0.25	0.43

* Adjusted by age, sex, race/ethnicity, education level, histology, tumor grade, calories, packyears, drinkday

Table 8. Adjusted Hazard Ratios of Flavonoid Intake and Overall Survival Among UADT Cancers, Stratified by rs1801282

Flavonoid Intake (mg/day)	Death/All	Non-Imputed Hazard Ratios CC aHR* (95% CI)	Non-Imputed Hazard Ratios CG + GG aHR* (95% CI)	Imputed Hazard Ratios CC aHR* (95% CI)	Imputed Hazard Ratios CG + GG aHR* (95% CI)
Total Flavonoid					
0 – 24.71	27/63	1.00	1.00	1.00	1.00
24.71– 53.57	50/113	1.13 (0.68-1.87)	1.70 (0.42-6.86)	0.99 (0.60-1.63)	1.55 (0.41-5.91)
53.57– 102.80	35/ 87	0.93 (0.52-1.64)	1.17 (0.30-4.53)	0.87 (0.52-1.45)	0.92 (0.27-3.14)
102.80+	30/81	1.16 (0.66-2.06)	***0.14 (0.02-0.87)***	1.01 (0.61-1.66)	0.41 (0.09-1.78)
P_{trend}		0.80	0.06	0.91	0.19
Flavones					
0 - 0.0025	40/83	1.00	1.00	1.00	1.00
0.0025 – 0.016	23/55	1.08 (0.64-1.83)	0.32 (0.07-1.52)	1.16 (0.71-1.89)	0.62 (0.15-2.46)
0.016 – 0.066	47/109	0.72 (0.42-1.23)	0.85 (0.21-3.37)	0.84 (0.51-1.38)	1.91 (0.56-6.55)
0.066 +	32/ 97	0.78 (0.45-1.36)	2.17 (0.49- 9.55)	0.81 (0.48-1.36)	1.80 (0.48-6.69)
P_{trend}		0.18	0.52	0.24	0.24
Flavonols					
0 – 3.28	20/59	1.00	1.00	1.00	1.00
3.28– 5.56	43/89	1.13 (0.64-1.99)	2.12 (0.43-10.60)	1.05 (0.63-1.76)	1.38 (0.34-5.51)
5.56– 8.46	46/103	1.01 (0.57-1.77)	1.17 (0.17-7.98)	0.96 (0.58-1.60)	0.82 (0.13-5.02)
8.46+	33/93	1.02 (0.55-1.88)	0.13 (0.01-1.44)	0.95 (0.56-1.61)	0.18 (0.03-1.24)
P_{trend}		0.91	0.05	0.73	***0.03***
Flavan-3-ols					
0 – 4.00	33/71	1.00	1.00	1.00	1.00
4.00– 12.43	43/96	0.78 (0.46-1.31)	2.38 (0.43-13.18)	0.87 (0.54-1.41)	2.41 (0.55-10.47)
12.43– 38.75	43/114	0.74 (0.44-1.27)	2.21 (0.38-12.80)	0.79 (0.47-1.33)	1.78 (0.38-8.25)
38.75+	23/63	0.82 (0.45-1.51)	0.49 (0.07-3.55)	0.82 (0.50-1.36)	0.82 (0.17-4.02)
P_{trend}		0.45	0.36	0.42	0.50
Flavanones					
0 – 4.18	40/83	1.00	1.00	1.00	1.00
4.18– 18.12	35/79	0.71 (0.41-1.22)	2.26 (0.50-10.15)	0.85 (0.50-1.45)	2.77 (0.69-11.09)
18.12– 40.68	36/100	0.79 (0.47-1.34)	0.59 (0.12-2.91)	0.89 (0.54-1.47)	0.76 (0.17-3.32)
40.68+	31/82	0.77 (0.45-1.30)	0.28 (0.06-1.32)	0.82 (0.50-1.34)	0.81 (0.23-2.84)
P_{trend}		0.41	***0.04***	0.49	0.36
Isoflavonoids					
0 – 0.017	26/68	1.00	1.00	1.00	1.00
0.017– 0.053	20/54	1.10 (0.58-2.06)	0.38 (0.09-1.52)	1.06 (0.61-1.85)	0.63 (0.19-2.09)
0.053– 0.23	48/94	1.19 (0.68-2.09)	***0.21 (0.05-0.84)***	1.06 (0.64-1.74)	0.39 (0.10-1.48)

0.23+	48/128	1.51 (0.84-2.71)	***0.03 (0.00-0.44)***	1.18 (0.69-2.02)	***0.10 (0.01-0.99)***
P_{trend}		0.17	***0.00***	0.58	***0.02***

* Adjusted by age, sex, race/ethnicity, education level, histology, tumor grade, calories, packyears, drinkday

Table 9. Adjusted Hazard Ratios of Flavonoid Intake and Overall Survival Among UADT Cancers Stratified by rs3856806

Flavonoid Intake (mg/day)	Death/All	Non-Imputed Hazard Ratios CC aHR* (95% CI)	Non-Imputed Hazard Ratios CT + TT aHR* (95% CI)	Imputed Hazard Ratios CC aHR* (95% CI)	Imputed Hazard Ratios CT + TT aHR* (95% CI)
Total Flavonoid					
0 – 24.71	27/64	1.00	1.00	1.00	1.00
24.71– 53.57	50/112	1.23 (0.74-2.06)	1.50 (0.42-5.46)	1.04 (0.63-1.74)	1.38 (0.37-5.11)
53.57– 102.80	36/88	0.94 (0.53-1.68)	0.98 (0.33-2.84)	0.93 (0.57-1.56)	0.98 (0.33-2.90)
102.80+	30/81	1.06 (0.59-1.93)	0.76 (0.22-2.60)	0.96 (0.57-1.60)	0.88 (0.25-3.10)
P_{trend}		0.90	0.54	0.28	0.69
Flavones					
0 - 0.0025	40/84	1.00	1.00	1.00	1.00
0.0025 – 0.016	23/ 55	1.26 (0.73-2.18)	0.55 (0.18-1.71)	1.22 (0.73-2.04)	0.69 (0.22-2.19)
0.016 – 0.066	47/108	0.95 (0.54-1.65)	0.38 (0.13-1.13)	0.98 (0.58-1.68)	0.50 (0.16-1.53)
0.066 +	33/98	1.03 (0.59-1.82)	0.47 (0.13-1.63)	0.96 (0.56-1.66)	0.53 (0.15-1.88)
P_{trend}		0.84	0.11	0.72	0.24
Flavonols					
0 – 3.28	20/60	1.00	1.00	1.00	1.00
3.28– 5.56	43/88	1.08 (0.60-1.93)	***3.83 (1.28-11.45)***	1.01 (0.60-1.70)	2.56 (0.87-7.54)
5.56– 8.46	46/103	0.95 (0.53-1.71)	1.18 (0.29-4.88)	0.94 (0.56-1.58)	0.91 (0.23-3.67)
8.46+	34/94	0.87 (0.46-1.66)	0.98 (0.28-3.43)	0.87 (0.51-1.50)	0.86 (0.26-2.87)
P_{trend}		0.55	0.79	0.55	0.56
Flavan-3-ols					
0 – 4.00	33/60	1.00	1.00	1.00	1.00
4.00– 12.43	43/ 88	0.90 (0.53-1.53)	0.87 (0.23-3.25)	0.99 (0.60-1.64)	0.94 (0.26-3.42)
12.43– 38.75	44/103	0.81 (0.47-1.39)	0.87 (0.22-3.41)	0.84 (0.50-1.43)	0.93 (0.24-3.54)
38.75+	23/94	0.73 (0.38-1.40)	0.88 (0.22-3.52)	0.82 (0.49-1.37)	1.03 (0.28-3.82)
P_{trend}		0.31	0.89	0.35	0.93
Flavanones					
0 – 4.18	40/71	1.00	1.00	1.00	1.00
4.18– 18.12	36/ 96	0.80 (0.46-1.38)	3.47 (0.92-13.00)	0.89 (0.52-1.52)	2.00 (0.50-8.01)
18.12– 40.68	36/115	0.88 (0.51-1.51)	0.74 (0.23-2.40)	0.94 (0.56-1.57)	0.76 (0.21-2.71)
40.68+	31/63	0.76 (0.43-1.32)	0.62 (0.20-1.92)	0.83 (0.49-1.39)	0.68 (0.22-2.10)
P_{trend}		0.41	0.13	0.54	0.27
Isoflavonoids					
0 – 0.017	26/83	1.00	1.00	1.00	1.00
0.017– 0.053	20/ 80	0.94 (0.48-1.84)	1.34 (0.46-3.88)	1.02 (0.57-1.81)	1.16 (0.40-3.37)
0.053– 0.23	48/100	1.24 (0.69-2.23)	0.92 (0.32-2.64)	1.14 (0.69-1.89)	0.77 (0.28-2.09)

0.23+	49/82	1.56 (0.85-2.86)	***0.17 (0.04-0.78)***	1.22 (0.71-2.09)	0.27 (0.06-1.27)
P_{trend}		0.10	0.06	0.41	0.09

* Adjusted by age, sex, race/ethnicity, education level, histology, tumor grade, calories, packyears, drinkday

Table 10. Interaction of Dichotomized Flavonoids and SNPS Among Lung Cancers

Flavonoid Intake (mg/day)	rs3734254 aHR* (95% CI)	rs10865710 aHR* (95% CI)	rs1801282 aHR* (95% CI)	rs3856806 aHR* (95% CI)
Total Flavonoid				
< 53.57	1.00	1.00	1.00	1.00
≥ 53.57	1.25 (0.92-1.71)	1.31 (0.96-1.80)	1.06 (0.83-1.37)	1.02 (0.79-1.32)
Interaction	***0.59 (0.37-0.96)***	***0.58 (0.37- 0.92)***	0.87 (0.47-1.63)	0.95 (0.55-1.62)
Flavones				
< 0.016	1.00	1.00	1.00	1.00
≥ 0.016	0.84 (0.62-1.14)	0.74 (0.54-1.01)	0.77 (0.60-0.99)	0.79 (0.61-1.02)
Interaction	1.06 (0.67-1.69)	1.51 (0.95-2.40)	2.17 (1.16-4.08)	1.40 (0.83-2.38)
Flavonols				
< 5.56	1.00	1.00	1.00	1.00
≥ 5.56	1.13 (0.82-1.55)	0.91 (0.67-1.25)	0.91 (0.67-1.25)	0.91 (0.67-1.25)
Interaction	***0.53 (0.33-0.84)***	0.82 (0.52-1.31)	0.82 (0.52-1.31)	0.82 (0.52-1.31)
Flavan-3-ols				
< 12.43	1.00	1.00	1.00	1.00
≥ 12.43	1.31 (0.96-1.79)	1.30 (0.95-1.78)	1.15 (0.90-1.47)	1.23 (0.95-1.59)
Interaction	0.66 (0.41-1.06)	0.68 (0.43-1.08)	0.97 (0.52-1.80)	0.68 (0.40-1.16)
Flavanones				
< 18.12	1.00	1.00	1.00	1.00
≥ 18.12	1.16 (0.85-1.57)	1.46 (1.06-1.99)	1.26 (0.98-1.62)	1.16 (0.90-1.51)
Interaction	1.02 (0.64-1.62)	***0.63 (0.40-1.00)***	0.67 (0.36-1.25)	1.02 (0.60-1.73)
Isoflavonoids				
< 0.053	1.00	1.00	1.00	1.00
≥ 0.053	1.18 (0.86-1.61)	1.29 (0.94-1.76)	1.00 (0.77-1.30)	1.06 (0.81-1.38)
Interaction	0.82 (0.52-1.31)	0.67 (0.43-1.06)	1.10 (0.59-2.05)	0.88 (0.52-1.49)

* Adjusted by age, sex, race/ethnicity, education level, histology, tumor grade, calories, packyears

Table 11. Interaction of Dichotomized Flavonoids and SNPS rs3734254 and rs10865710 Among UADT Cancers

	rs3734254		rs10865710	
Flavonoid Intake (mg/day)	Non-Imputed aHR (95% CI)	Imputed aHR (95% CI)	Non-Imputed aHR (95% CI)	Imputed aHR (95% CI)
Total Flavonoid				
< 53.57	1.00	1.00	1.00	1.00
≥ 53.57	0.89 (0.31-2.59)	0.85 (0.59-1.22)	0.78 (0.47-1.30)	0.81 (0.53-1.23)
Interaction	0.89 (0.41-1.90)	1.00 (0.53-1.87)	1.04 (0.51-2.09)	1.18 (0.64-2.18)
Flavones				
< 0.016	1.00	1.00	1.00	1.00
≥ 0.016	0.35 (0.12-1.05)	0.91 (0.62-1.34)	0.77 (0.46-1.27)	0.94 (0.60-1.47)
Interaction	1.89 (0.87-4.08)	1.24 (0.64-2.37)	1.21 (0.60-2.44)	1.07 (0.57-2.00)
Flavonols				
< 5.56	1.00	1.00	1.00	1.00
≥ 5.56	0.91 (0.67-1.25)	0.90 (0.61-1.33)	0.92 (0.56-1.54)	0.79 (0.51-1.24)
Interaction	0.82 (0.52-1.31)	0.76 (0.38-1.52)	0.76 (0.37-1.57)	1.09 (0.61-1.98)
Flavan-3-ols				
< 12.43	1.00	1.00	1.00	1.00
≥ 12.43	0.89 (0.31-2.60)	0.91(0.63-1.32)	0.76 (0.46-1.28)	0.76 (0.48-1.19)
Interaction	0.93 (0.43-1.98)	0.83 (0.40-1.75)	1.43 (0.71-2.88)	1.33 (0.72-2.46)
Flavanones				
< 18.12	1.00	1.00	1.00	1.00
≥ 18.12	0.89 (0.30-2.62)	0.87 (0.60-1.26)	0.98 (0.59-1.61)	0.91 (0.58-1.44)
Interaction	0.87 (0.41-1.85)	0.89 (0.45-1.78)	0.68 (0.33-1.37)	0.82 (0.43-1.56)
Isoflavonoids				
< 0.053	1.00	1.00	1.00	1.00
≥ 0.053	2.19 (0.71-6.72)	1.04 (0.71-1.54)	1.48 (0.85-2.57)	1.07 (0.68-1.68)
Interaction	0.65 (0.30-1.40)	0.87 (0.45-1.67)	0.69 (0.33-1.44)	0.83 (0.44-1.55)

* Adjusted by age, sex, race/ethnicity, education level, histology, tumor grade, calories, packyears, drinkday

Table 12. Interaction for Dichotomized Flavonoids and SNPS rs1801282 and rs3856806 Among UADT Cancers

Flavonoid Intake (mg/day)	rs1801282 aHR (95% CI)	rs1801282 Imputed aHR (95% CI)	rs3856806 aHR (95% CI)	rs3856806 Imputed aHR (95% CI)
Total Flavonoid				
< 53.57	1.00	1.00	1.00	1.00
≥ 53.57	0.95 (0.64-1.40)	0.89 (0.65-1.23)	0.87 (0.59-1.29)	0.86 (0.63-1.18)
Interaction	0.49 (0.19-1.24)	0.87 (0.37-2.04)	0.85 (0.38-1.91)	1.05 (0.51-2.16)
Flavones				
< 0.016	1.00	1.00	1.00	1.00
≥ 0.016	0.72 (0.49-1.05)	0.92 (0.65-1.29)	0.88 (0.60-1.29)	0.99 (0.70-1.41)
Interaction	1.94 (0.77-4.91)	1.41 (0.62-3.23)	0.74 (0.33-1.67)	0.90 (0.43-1.88)
Flavonols				
< 5.56	1.00	1.00	1.00	1.00
≥ 5.56	0.92 (0.63-1.34)	0.86 (0.61-1.22)	0.89 (0.61-1.31)	0.93 (0.73-1.17)
Interaction	***0.36 (0.14-0.97)***	0.74 (0.31-1.77)	0.62 (0.27-1.44)	0.99 (0.60-1.62)
Flavan-3-ols				
< 12.43	1.00	1.00	1.00	1.00
≥ 12.43	0.90 (0.61-1.32)	0.87 (0.62-1.23)	0.84 (0.56-1.24)	0.82 (0.58-1.15)
Interaction	0.66 (0.26-1.66)	1.00 (0.44-2.31)	1.01 (0.44-2.30)	1.31 (0.64-2.66)
Flavanones				
< 18.12	1.00	1.00	1.00	1.00
≥ 18.12	0.90 (0.61-1.31)	0.87 (0.63-1.20)	0.88 (0.60-1.29)	0.88 (0.63-1.24)
Interaction	0.46 (0.18-1.18)	0.75 (0.33-1.69)	0.60 (0.26-1.36)	0.74 (0.36-1.56)
Isoflavonoids				
< 0.053	1.00	1.00	1.00	1.00
≥ 0.053	1.34 (0.89-2.00)	1.05 (0.73-1.51)	1.47 (0.97- 2.23)	1.09 (0.76- 1.57)
Interaction	***0.38 (0.15-0.97)***	0.67 (0.28-1.56)	***0.35 (0.15-0.83)***	0.58 (0.27-1.26)

* Adjusted by age, sex, race/ethnicity, education level, histology, tumor grade, calories, packyears, drinkday

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