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Variations in bitter-taste receptor genes, dietary intake, and colorectal adenoma risk

Susan M. Schembre, PhD, RD^{1,*}, Iona Cheng, PhD, MPH², Lynne R. Wilkens, DrPH², Cheryl L. Albright, PhD, MPH³, and Loïc Le Marchand, MD, PhD²

¹Department of Behavioral Science, The University of Texas MD Anderson Cancer Center, Houston, Texas, 77030, USA

²Epidemiology Program, University of Hawaii Cancer Center, Honolulu, Hawaii 96813, USA

³School of Nursing and Dental Hygiene, University of Hawaii at Manoa, Honolulu, Hawaii 96813

Abstract

Genetic variants in bitter-taste receptor genes have been hypothesized to negatively impact health outcomes and/or influence dietary intake and, consequently, could increase the risk of colorectal neoplasia. Using a case-control study of 914 colorectal adenoma cases/1188 controls, we explored associations among colorectal adenoma risk, dietary intake, and genetic variation in three bitter-taste receptor genes: *TAS2R38* (rs713598, rs1726866, rs10246939), *TAS2R16* (rs846672), and *TAS2R50* (rs1376251). Analysis of covariance was conducted to detect trends in dietary intake across *TAS2R* genotypes/haplotypes. Odds ratios and 95% confidence intervals were estimated by logistic regression to test gene-adenoma risk associations. No significant associations were observed between the *TAS2R38* PAV/PAV diplotype or the *TAS2R16* (rs846672) polymorphism with the selected diet variables. We observed weak inverse associations between the *TAS2R50* (rs1376251) C allele and dietary fiber and vegetable intake (P s < 0.015). Odds ratios for adenoma risk were not significantly different from the null. Our findings do not support a link between these *TAS2R* genotypes/haplotypes and dietary intake that could impact colorectal adenoma risk. However, given the paucity of data, we cannot dismiss the possibility that these genes may influence colorectal adenoma risk in other ways, such as through impaired gastrointestinal function, particularly in subgroups of the population.

Introduction

Genetic variation in type 2 bitter-taste receptors (*TAS2R*) may influence health-related outcomes. More than 25 functional *TAS2R* genes are clustered on chromosomes 5, 7, and 12 that respond to bitter tastants (e.g., thiocyanate and -glucopyranosides) (1, 2) and are expressed within the oral cavity (3), the gastrointestinal mucosa (4), and the lungs (5). *TAS2R* variants are hypothesized to play roles in individuals' food preferences (6, 7) and the neutralization and expulsion of toxins from the colon/rectum (8), thereby influencing cancer risk.

Variants of at least three *TAS2R* genes have been linked to poor dietary intake or increased chronic disease risk. The most commonly studied of these genes, *TAS2R38* (rs713598, rs1726866, rs10246939) is most commonly studied. The *TAS2R38* PAV/PAV diplotype (the "taster" diplotype) explains 60% - 85% of the variance in taste sensitivity to the thiocyanate-containing chemicals, phenylthiocarbamide (PTC) and 6-n-propylthiouracil

*Corresponding author. Tel: +01 563 5858; Fax: +01 563 9760; sschembre@mdanderson.org.

(PROP) (9-11). Yet, research does not consistently demonstrate associations of PTC/PROP sensitivity or genetic variation of *TAS2R38* with a lower intake of bitter-tasting (12-14).

Two other *TAS2R* genes, *TAS2R16* (rs846672) and *TAS2R50* (rs1376251), could similarly influence the risk of colorectal adenoma. *TAS2R16* codes for α -glucopyranosides taste sensitivity (15) and has been linked with greater alcohol intake and dependence (16-18) given that excessive alcohol use is a risk factor for colorectal cancer (19). *TAS2R50*, a gustducin-linked G-protein, also plays a role in the detection of bitter stimuli. *TAS2R50* has been controversially linked with an increased risk of myocardial infarction (20-23) through a hypothesized but untested association with poor dietary intake (24, 25). Despite inconsistencies in the research, the consensus is that genetic variants of *TAS2R* bitter-taste receptor genes can influence dietary intake in a way that might impact disease risk, including colorectal neoplasia (a common precursor lesion for colorectal cancer) (6). Therefore, it is reasonable to hypothesize that genetic variations of the *TAS2R* genes are associated with colorectal adenoma risk.

Basson and colleagues (26) have recently explored the cross-sectional association between taste sensitivity to PTC/PROP, a phenotype the PAV haplotype, and number of histologically confirmed neoplastic polyps in 251 asymptomatic men age 28 to 87 years. Their findings demonstrated a small but positive correlation between perceived PTC/PROP bitterness and number of polyps, particularly among men greater than 66 year old ($r = 0.24$, $P < 0.01$) suggesting that genetic sensitivity to bitter taste may influence colon cancer risk in older men. Conversely, Carrai and colleagues (27) showed that the *TAS2R38* AVI/AVI diplotype (the “non-taster” diplotype) was positively associated with an increased risk of colorectal cancer in a large case-control study of Czech Republic and Germany residents ($OR_{pooled} = 1.34$; 95% CI, 1.12, 1.61; $P = 0.001$). Rather than a diet-related link, it was hypothesized that the AVI/AVI diplotype could be a biomarker for the impaired function of the gastrointestinal tract resulting in a slower elimination of toxins from the gut. Due to conflicting findings such as these, it remains unclear whether genetic variation in *TAS2R* genes influences colorectal cancer risk.

The present case-control study examined the associations between genetic variants of *TAS2R16*, *TAS2R38*, and *TAS2R50* with dietary intakes of fiber- and antioxidant-rich fruits and vegetables, alcohol consumption, and risk of colorectal adenoma in a multi-ethnic sample of men and women. In line with the approach of Basson and colleagues described above (26), genetic variants of bitter-taste receptor genes were hypothesized to be associated with poor dietary intake, including decreased vegetable intake (*TAS2R38* PAV haplotype and *TAS2R50* C allele) and/or greater alcohol consumption (*TAS2R16* A allele) and, as the result, with an increased risk of colorectal adenoma.

Materials and methods

Subjects

The study design and data collection procedures for this colorectal adenoma study have been described in detail elsewhere (28). In brief, colorectal adenoma cases were recruited in two phases. Cases were identified via adenoma screening by flexible sigmoidoscopy from July 1996 to February 2000 at the Hawai'i site of the Prostate Lung Colorectal and Ovarian (PLCO) screening trial and from January 1995 to June 2006 at the Gastroenterology Screening Clinic of Kaiser Permanente Hawai'i. Starting in June 2002, recruitment also included patients undergoing colonoscopy in the Kaiser Permanente Gastroenterology Department. Eligible cases were patients of Japanese American, white, or Native Hawaiian race/ethnicity with histologically confirmed, first-time, adenomas of the colorectum. Controls were recruited among patients found to have a normal colon and rectum at

endoscopy and were individually matched to the cases on age, sex, race/ethnicity, screening date (± 3 months), recruitment site, and type of examination. The participation rate was 67.8% for cases and 69.2% for controls. Blood samples were collected from 93% of the eligible participants. The present analyses were based on 914 colorectal adenoma cases and 1,188 controls with available DNA. Institutional review board approval was obtained from each of the participating institutions and informed consent was provided by all study participants.

Questionnaire data

Demographic and lifestyle data were collected via an interview-administered questionnaire that included questions regarding lifetime histories of smoking, vitamin and mineral supplement use, and usual physical activity, a family history of colorectal cancer, as well as current weight and height. The interview also included a validated food frequency questionnaire with 268 food items and categories (29). Participants were asked to report the frequency and amount of each food consumed during the year prior to their endoscopic examination. For this study, we focused on the following eight categories of tart- or bitter-tasting foods and beverages demonstrated in previous studies to vary with *TAS2R* genotypes/haplotypes and/or to be associated with colorectal cancer risk: total dietary fiber, vegetables (all), vegetables (no legumes, denoted “non-starchy vegetables”), dark green vegetables (including dark green cruciferous vegetables, taro leaves, spinach, dark green lettuce, peppers, other dark green vegetables), cruciferous vegetables (including broccoli, cauliflower, cabbage, won bok, dark green cruciferous, light green cruciferous, and other cruciferous), fruits (all), citrus fruits (including oranges, grapefruit, tangerines, other citrus fruits, grapefruit juice, orange juice, lime and lemon juice), and alcohol (including beer, wine, hard liquor, and other alcohol).

SNP Selection

Five non-synonymous (missense) SNPs of three bitter-taste receptor genes (*TAS2R38*, *TAS2R50*, *TAS2R16*) expressed in the oral cavity were selected for genotyping based on previously published research (13, 16-18, 20, 24, 25, 30, 31). For *TAS2R38*, we selected three of the most commonly studied SNPs (rs713598, rs1726866, and rs10246939). For *TAS2R50*, we selected the rs1376251 polymorphism. For *TAS2R16* gene, we considered the two non-synonymous SNPs: rs846664 and rs860170 polymorphisms (32, 33) and chose to include rs860170 because of its greater minor allele frequency in whites. However, the genotype distribution for rs860170 was not in Hardy-Weinberg equilibrium for any of the three ethnic groups sampled in this study ($P < 0.001$); thus, a proxy SNP (rs846672) was genotyped that was highly correlated with rs860170 ($r^2 = 1$ in European (HapMap CEU) and Japanese (HapMap JPT) (32, 33). Each of the selected SNPs had minor allele frequencies greater than 5% in each racial/ethnic group.

Genotyping

Genotyping was conducted by the 5' nuclease Taqman allelic discrimination assay using the manufacturer's pre-designed primer/probe sets, and assays were read on a 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). All assays were carried out by individuals blinded to case-control status. For quality control, 177 blind replicate samples were included. The average concordance rate among these samples was 92.7%. The average genotyping success rate for the SNPs was 99.1%. The final set of SNPs were all in Hardy-Weinberg equilibrium at the $P > 0.01$ level for each racial/ethnic group.

Statistics

Analysis of covariance was conducted to estimate trends in mean dietary intakes by *TAS2R* genotypes/haplotypes (gene-diet associations) and across ethnic/racial groups. Dietary variables were adjusted for total energy intake by the method of residuals (34) and are presented as geometric means. Models were minimally adjusted for sex, race/ethnicity, and age. To ensure that confounders did not bias the estimates, a model fully adjusted for the following additional variables was also performed and the results compared smoking status, pack-years of cigarette smoking, case-control status, as well as family history of colorectal cancer among first degree relatives. Because of multiple tests, the type I error was inflated. Therefore, the critical value for statistical significance was corrected by the Bonferroni method to $p = 0.001$ ($0.05/5$ SNPs \times 8 diet variables = $0.05/40$) to control for the multiple comparisons for the gene-diet associations.

Odds ratios (OR) and 95% confidence intervals (95% CI) for the associations between *TAS2R* genotypes/haplotypes and colorectal adenoma risk (gene-risk associations) were estimated by unconditional logistic regression, minimally adjusting for recruitment site, index endoscopy type, age at exam, sex, and race/ethnicity. Gene-by-diet interactions on adenoma risk were additionally tested. To assess the effect of confounding, regression models were further adjusted for other adenoma risk factors: family history of colorectal cancer, vitamin supplement use, years of education, smoking status, pack-years of cigarette smoking, lifetime physical activity, and body mass index. P-values for both the partially- and fully-adjusted models are presented. However, there was little effect of including these variables in the models (change in beta estimates <10%) and the fully adjusted odds ratios are not presented. The variants were parameterized as dummy variables representing each genotype and as continuous trends assigned the dosage of haplotype or variant allele.

TAS2R haplotype frequencies among adenoma cases and controls were estimated following the methods of Stram et al. (35). Haplotype dosage (i.e. an estimate of the number of copies of haplotype *h*) for each individual and each haplotype, *h*, was computed using that individual's genotype data and haplotype frequency estimates as obtained from the E-M algorithm (36). Statistical significance for the gene-risk associations was corrected by the Bonferroni method to $p = 0.0025$ ($0.05/5$ SNPs \times 4 tests (all and by race/ethnicity = $0.05/20$)) to address the issue of multiple comparisons testing for the five SNPs and four tests (all and by race/ethnicity). Statistical significance for the gene-by-diet interactions on adenoma risk was also corrected to $p = 0.00625$ ($0.05/8$ tests).

Results

Participant characteristics

Table 1 summarizes participant characteristics by adenoma case and control status. Compared to cases, controls were less likely to smoke ($P < 0.001$) or to have a family history of colorectal cancer ($P = 0.010$), were more likely to take vitamin supplements ($P = 0.003$), and had a lower mean BMI compared to cases ($P < 0.001$) without a difference in mean reported energy intake ($P = 0.903$) or lifetime physical activity participation ($P = 0.184$). Compared to controls, cases had significantly lower intakes of dietary fiber ($P < 0.001$), total vegetables ($P = 0.043$), total fruits ($P < 0.001$), and citrus fruits ($P = 0.006$), and a significantly greater alcohol consumption ($P = 0.002$). We also observed differences in all dietary variables by race/ethnicity ($P < 0.005$) with the exception of cruciferous vegetable intake ($P = 0.709$) (Supplementary Table 1). Japanese Americans tended to consume the lowest amounts of vegetables, whereas whites consumed the greatest amounts of dark green vegetables, fruit, and alcohol.

TAS2R genotypes/haplotypes

Four of the eight possible *TAS2R38* haplotypes (combination of rs713598, rs1726866, and rs10246939 genotypes) were observed in our study. The two most common haplotypes were AVI (47.7%; “non-taster” haplotype) and PAV (49.4%; “taster” haplotype). The AAV and AAI haplotypes were rare (2.7% and <1%, respectively), and participants with one or two copies of these haplotypes were excluded from the *TAS2R38* analyses. The other possible haplotypes, PAI, PVI, PVV, and AVV, were not observed in this sample. The most frequently observed combination of haplotypes was the heterozygous PAV/AVI diplotypes (46.6%) followed by PAV/PAV (“tasters”; 27.8%) and AVI/AVI (“non-tasters”; 25.6%). The overall genotype frequencies for *TAS2R16* (rs846672) and *TAS2R50* (rs1376251) were AA=11.7%, AC=46.1% and CC=42.2%, and CC=26.2%, TC=44.2%, and T/T=29.6%, respectively (Table 2).

All genotypes/haplotype distributions varied significantly by race/ethnicity ($P < 0.001$), with the *TAS2R38* PAV/PAV diplotypes most common in Japanese Americans (38.8%), followed by whites (30.7%) and Native Hawaiians (30.5%). The AA genotype for rs846672 was most common in Japanese Americans (61.6%), followed by Native Hawaiians (24.6%) then whites (13.8%) and, whereas the CC genotype for rs1376251 was most frequent in whites (81.3%), followed by Native Hawaiians (11.5%) and Japanese Americans (7.2%).

TAS2R and Dietary Intake

Table 3 summarizes the gene-diet analyses for all study participants combined. Accounting for the adjusted $P = 0.001$ level, only nominally significant negative associations between the *TAS2R50* rs1376251 C allele and consumption of dietary fiber ($P_{\text{full-adj}} = 0.013$), vegetables ($P_{\text{full-adj}} = 0.004$), and non-starchy vegetables (vegetables not including legumes) ($P_{\text{full-adj}} = 0.026$) were also observed (Table 3). No significant race/ethnicity-by-genotype/haplotype or sex-by-genotype/haplotype interactions were observed (not shown). Race/ethnicity-specific gene-diet tables are presented in Supplementary Tables 3a-3c.

TAS2R and Colorectal Adenoma Risk

We observed no significant associations between the *TAS2R16*, *TAS2R38*, or *TAS2R50* haplotypes/genotypes and colorectal adenoma risk for the combined sample at the corrected $P = 0.0025$ level (Table 4). No significant race/ethnicity-by-genotype/haplotype or sex-by-genotype/haplotype interactions were observed (not shown).

TAS2R by diet interactions on Colorectal Adenoma Risk

Accounting for the adjusted $P = 0.00625$, only one gene-by-diet interaction effect was borderline significant: citrus fruit ($P = 0.007$) for *TAS2R50*. However, there were no discernible patterns of associations that coincided with any plausible hypotheses.

Discussion

Few studies have explored associations between variants of bitter-taste receptor genes and colorectal adenoma risk (27, 37) and none have included a measure of dietary intake. This study examined associations of three bitter-taste receptor genes (*TAS2R16*, *TAS2R38*, and *TAS2R50*) with colorectal adenoma risk in a multi-ethnic sample of whites, Japanese Americans, and Native Hawaiians. We observed only weak gene-diet associations between the *TAS2R50* C allele (rs1376251) and decreasing intakes of dietary fiber and vegetables, none of the gene-adenoma risk reached significance, and there were no meaningful gene-by-diet interactions on adenoma risk.

The tested gene-diet associations provided little support for an influence of bitter-taste receptor genes on dietary intake. We hypothesized a negative association between the *TAS2R38* PAV haplotype and selected dietary variable, including cruciferous vegetable intake (13, 16). However, we were unable to confirm this association despite having adequate power to detect significant trends [greater than 99% to detect an $R^2 = 0.02$ at $\alpha = 0.001$ for a SNP with a minor allele frequency (MAF) of 0.05 or greater]. A positive association between the A allele of the *TAS2R16* SNP (rs846672) and alcohol intake was also hypothesized (16), but not confirmed. Lastly, we hypothesized the *TAS2R50* (rs1376251) C allele would be associated with decreasing consumption of fruits/vegetables and/or an increasing consumption of alcohol (24, 25). Yet, only nominally significant trends were detected in the hypothesized direction for dietary fiber and vegetable consumption. It should be noted that a lack of support for these hypotheses is potentially due to industry food processing (38) and home preparation techniques, such as prolonged cooking or the addition of salt, sugar, or fat (30, 39, 40), that “de-bitter” foods to make them more palatable. Ultimately, our findings provide limited support that genetic variants of the *TAS2R* taste receptors gene family can influence dietary intake to the extent that there is a subsequent impact on colorectal adenoma risk.

A limited number of studies have explored associations between *TAS2R* genotypes and colorectal cancer risk. In one study, Carrai and colleagues (27) explored the association between *TAS2R38* SNPs and diplotypes, and colorectal cancer among predominantly white 1,203 colorectal cases and 1,332 controls. Findings demonstrated an increased risk of colorectal cancer for the AVI/AVI group (“non-tasters”) compared to the PAV/PAV group (“tasters”) (OR = 1.34; 95% CI, 1.12, 1.61; $P = 0.001$). This observed direction of association is opposite of what would be consistent with our diet-related hypothesis that “tasters” would be at greater risk of colorectal adenoma risk due to a decreased intake of the chemoprotective nutrients found in bitter-tasting foods. Rather, they suggested that the AVI/AVI diplotype could be a biomarker for an impaired gastrointestinal function (27). In the current study, the odds ratio and confidence interval for whites with the AVI/AVI diplotype compared to the PAV/PAV (OR = 1.33, 95% CI 0.91, 1.97) very similar to that observed by Carrai and colleagues. Unfortunately, we did not have sufficient power to detect this as significant in race/ethnicity-specific analyses. Despite this limitation, our findings for the *TAS2R38* gene align with a diet-related hypothesis rather than with Carrai and colleague's biomarker hypothesis. Further consideration of race/ethnicity-disparate associations between the *TAS2R38* AVI/AVI diplotype as a biomarker for elevated colorectal cancer risk is warranted.

Our study is strengthened by the multi-ethnic composition of the sample, as well as the examination of dietary intake as a possible phenotypic link between variations in bitter-taste receptor genes and colorectal cancer risk. Compared to prior studies of predominantly European populations, our multi-ethnic study is characterized by a substantial variation in intake, presumably increasing the power of our study to detect gene-diet associations. However, inherent dietary measurement error and the lack of detailed food preparation techniques could ultimately have attenuated observed associations. Another limitation was our inability to explore associations by race/ethnicity, due to having limited statistical power. Limited statistical power, especially in subgroups, also precluded us from firm conclusions on whether there is a true lack of association between the *TAS2R* SNPs genotyped in this study and risk of colorectal adenoma (80% power to detect an OR = 0.73 for a SNP with a MAF of 0.25 using a log additive model with $\alpha = 0.0025$). Despite these limitations, the magnitudes of gene- risk association observed in this study may still have clinical relevance.

In summary, our findings in combination with others' offer limited support for associations among variations of selected *TAS2R* genes, dietary intakes, and colorectal adenoma risk. Only nominal gene-diet trends were observed between the *TAS2R50C* allele and decreasing dietary fiber and vegetable intake. Given these findings, we conclude that the influence of variants of the selected bitter-taste receptor genes on dietary intake is unlikely to be substantial enough to influence colorectal adenoma risk negatively. Gene-risk associations for variations of each *TAS2R* gene were non-significant as were the gene-by-diet interactions on adenoma risk. Given the paucity of studies in this area, we cannot discount possible weak associations, especially in population subgroups. While bitter-taste receptor genes may not have a meaningful impact on dietary intake, we also cannot dismiss the possibility they may play other important roles related to colorectal cancer risk, particularly in subgroups of the population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Study characteristics of colorectal adenoma cases and controls

	Case (n=914)	Control (n=1188)	P-value
Males, %	60.2	62.7	0.236
Race, %			
Japanese American	31.8	32.6	
White	46.8	47.6	0.708
Native Hawaiian	21.3	19.9	
Smoking Status, %			
Never	41.8	51.9	
Past	44.5	40.8	<0.001
Current	13.7	7.3	
Procedure type, %			
Colonoscopy	42.9	30.3	
Flexible sigmoidoscopy	57.1	69.6	<0.001
Family history of colorectal cancer, %	17.6	13.6	0.010
Vitamin supplement use, % [†]	67.2	75.2	0.003
Age at exam, yr	60.6±8.8	60.6±8.4	0.947
Education, yr	15.1±3.4	15.4±3.1	0.090
Pack-years, No.	17.3±25.8	12.2±22.0	<0.001
BMI at exam, kg/m ²	28.0±5.9	26.8±5.0	<0.001
Lifetime physical activity, hr	11855±16072	11030±12406	0.184
Total energy, kcal/day ^{††}	2270±1091	2276±1173	0.903
Dietary fiber, g/day	20.8±7.0	22.2±7.6	<0.001
Total vegetables, g/day	359.1±168.9	375.1±184.8	0.043
Vegetables (no legumes), g/day	314.3.1±147.0	324.8±159.0	0.126
Cruciferous vegetables, g/day	48.3±51.4	47.1±43.9	0.779
Dark green vegetables, g/day	60.3±54.1	60.2±57.8	0.691
Total fruits, g/day	294.4±221.8	333.9±235.1	<0.001
Citrus fruits, g/day	87.9±114.1	100.0±128.4	0.006
Alcohol, mg/day	228.6±445.9	161.3±331.1	0.002

Categorical data are presented as percentages and continuous data are presented as means ± SD as indicated.

Pack-years = number of cigarettes smoked per day/20 × duration of smoking in years.

Supplement use = within the past 2 weeks

[†] n=2065 due to missing data.

^{††} n=2096 due to missing data.

Table 2
TAS2R haplotype/genotype frequencies (%) overall and by race/ethnicity (N=2102)

	Japanese Americans		Whites		Native Hawaiians		All (n=1964)
	Controls (n=383)	Cases (n=288)	Controls (n=500)	Cases (n=383)	Controls (n=223)	Cases (n=187)	
TAS2R38							
AVI/AVI	21.2	18.6	35.7	33.8	10.6	14.4	25.6
PAV/AVI	47.3	47.6	46.3	44.2	46.0	45.5	46.6
PAV/PAV	31.5	33.8	18.0	22.1	43.4	40.1	27.8
TAS2R16 (rs846672)							
	Controls (n=383)	Cases (n=290)	Controls (n=560)	Cases (n=427)	Controls (n=236)	Cases (n=193)	All (n=2089)
CC	28.7	36.2	47.9	49.2	50.4	47.1	42.2
AC	51.4	44.1	43.8	38.4	43.2	45.1	46.1
AA	19.9	19.7	8.4	12.4	6.4	7.8	11.7
TAS2R50 (rs1376251)							
	Controls (n=383)	Cases (n=290)	Controls (n=557)	Cases (n=425)	Controls (n=233)	Cases (n=194)	All (n=2082)
TT	58.6	55.5	8.6	8.9	32.2	40.7	29.6
TC	36.4	37.9	45.4	49.2	54.1	44.3	44.2
CC	5.0	6.6	46.0	41.9	13.7	15.0	26.2

Using the chi-square test, all genotype/haplotype distributions were found to vary significantly by race/ethnicity ($P < 0.001$)

Table 3
Association between TAS2R haplotypes/genotypes and select mean dietary intakes[†]

TAS2R38	AVI/AVI (n=499)		PAV/AVI (n=916)		PAV/PAV (n=570)		<i>P</i> _{full-adj} ^{††}
	Mean	95% CI	Mean	95% CI	Mean	95% CI	
Dietary fiber	19.1	19.0,19.1	19.4	19.3,19.5	19.1	19.1,19.2	0.929
Vegetables	340.1	339.7,340.5	342.7	342.4,343.0	347.4	347.1,347.8	0.478
Vegetables (no legumes)	295.7	295.3,296.1	295.9	295.6,296.2	305.0	304.6,305.3	0.288
Dark green vegetables	48.6	48.3,48.8	49.8	49.6,50.0	51.7	51.4,51.9	0.244
Cruciferous vegetables	36.3	36.0,36.5	37.0	36.9,37.2	40.7	40.5,41.0	0.047
Fruit	253.2	252.6,253.8	270.6	270.1,271.0	253.8	253.3,254.3	0.963
Citrus fruits	57.9	57.4,58.4	60.3	60.0,60.7	59.1	58.6,59.5	0.842
Alcohol (mg/d)	61.2	62.3,64.1	53.3	52.6,54.0	57.9	57.1,58.7	0.628

TAS2R16 (rs846672)	CC (n=903)		AC (n=923)		AA (n=263)		<i>P</i> _{full-adj}
	Mean	95% CI	Mean	95% CI	Mean	95% CI	
Dietary fiber	19.5	19.5,19.6	19.2	19.2,19.3	18.8	18.7,18.9	0.144
Vegetables	346.5	346.2,346.8	342.0	341.7,342.3	342.5	341.9,343.0	0.607
Vegetables (no legumes)	299.7	299.4,299.9	296.7	296.5,297.0	300.8	300.3,301.3	0.922
Dark green vegetables	52.0	51.8,52.2	48.3	48.1,48.45	49.9	49.5,50.2	0.181
Cruciferous vegetables	39.4	39.2,39.6	36.5	36.3,36.7	39.2	38.8,39.6	0.422
Fruit	268.7	268.3,269.1	260.0	259.6,260.5	250.2	249.4,250.9	0.168
Citrus fruits	60.4	60.0,60.8	61.0	60.6,61.4	49.6	48.9,50.3	0.169
Alcohol (mg/d)	59.8	59.1,60.5	57.1	56.5,57.8	50.5	49.2,51.7	0.405

TAS2R50 (rs1376251)	TT (n=625)		TC (n=923)		CC (n=533)		<i>P</i> _{full-adj}
	Mean	95% CI	Mean	95% CI	Mean	95% CI	
Dietary fiber	19.4	19.4,19.5	19.6	19.6,19.7	18.4	18.3,18.4	0.027
Vegetables	355.4	355.0,355.8	345.9	345.6,347.2	323.2	322.8,323.6	0.005
Vegetables (no legumes)	306.1	306.1,306.7	299.3	299.1,299.6	285.0	284.6,285.4	0.028
Dark green vegetables	50.5	50.2,50.7	50.7	50.5,50.9	48.5	48.2,48.8	0.508
Cruciferous vegetables	38.8	38.6,39.0	38.3	38.1,38.5	37.2	36.9,37.5	0.521
Fruit	265.8	265.3,266.4	263.4	263.0,263.8	255.1	254.4,255.7	0.447

<i>TAS2R38</i>	AVI/AVI (n=499)		PAV/AVI (n=916)		PAV/PAV (n=570)		$P_{\text{full-adj}}^{\dagger\dagger}$
	Mean	95% CI	Mean	95% CI	Mean	95% CI	
Citrus fruits	58.9	58.4,59.4	58.5	58.1,58.9	61.7	61.1,62.2	0.774
Alcohol (mg/d)	64.5	63.6,65.3	54.8	54.1,55.5	53.8	52.8,54.8	0.478

The p for trend is based on the F test (general linear models) for a variable assigned the dosage of the haplotype or variant allele.

[†] Dietary variables are presented as geometric means (grams/day unless otherwise noted) and are energy-adjusted.

^{††} Mean intakes are partially adjusted for case status, race, age, and sex and fully adjusted for case status, race, age, sex, smoking status, lifetime smoking (pack-years), and family history of colorectal cancer.

Table 4
Association between *TAS2R* haplotypes/genotypes and colorectal adenoma risk (N=2102)

	All												Whites						Native Hawaiians						Race/Ethnicity-by-Gene Interaction [†]														
	Controls n (%)			Case n (%)			OR (95% CI)			<i>P</i> -part-adj			<i>P</i> -full-adj			Controls n (%)			Case n (%)			OR (95% CI)			<i>P</i> -part-adj			<i>P</i> -full-adj			<i>P</i> -part-adj			<i>P</i> -full-adj					
<i>TAS2R38</i>																																							
AVIAVI	288 (25.6)	211 (24.5)	1.00 (reference)	82 (21.2)	54 (18.6)	1.00 (reference)	0.963	0.990	0.429	0.503	0.429	0.464	0.464	182 (35.7)	130 (33.8)	1.00 (reference)	0.924	0.893	0.196	0.280	0.196	0.280	0.215	0.155	98 (43.4)	75 (40.1)	1.00 (reference)	0.662	0.664	0.199	0.199	0.145	0.145	0.126	0.075	0.126	0.075	0.356	0.261
PAV/AVI	523 (46.6)	395 (45.6)	1.00 (0.80,1.25)	183 (47.3)	138 (47.6)	1.15 (0.76,1.75)	0.963	0.990	0.429	0.503	0.429	0.464	0.464	236 (46.3)	170 (44.2)	0.99 (0.73,1.34)	0.924	0.893	0.196	0.280	0.196	0.280	0.215	0.155	104 (46.0)	85 (43.5)	0.94 (0.34,1.21)	0.662	0.664	0.199	0.199	0.145	0.145	0.126	0.075	0.126	0.075	0.356	0.261
PAV/PAV	312 (27.8)	258 (29.9)	1.09 (0.84,1.40)	122 (31.5)	98 (33.8)	1.19 (0.77,1.85)	0.446	0.427	0.429	0.503	0.429	0.464	0.464	92 (18.0)	85 (22.1)	1.27 (0.87,1.86)	0.438	0.448	0.464	0.464	0.464	0.464	0.438	0.448	98 (43.4)	75 (40.1)	0.60 (0.32,1.15)	0.662	0.664	0.199	0.199	0.145	0.145	0.126	0.075	0.126	0.075	0.356	0.261
<i>TAS2R16</i> (rs846672)																																							
CC	497 (42.2)	406 (44.6)	1.00 (reference)	110 (28.7)	105 (36.2)	1.00 (reference)	0.132	0.116	0.955	0.948	0.955	0.484	0.484	268 (47.9)	210 (49.2)	1.00 (reference)	0.042	0.110	0.250	0.250	0.250	0.250	0.398	0.671	47 (8.4)	53 (12.4)	1.38 (0.89,2.15)	0.662	0.664	0.581	0.581	0.573	0.604	0.707	0.664	0.707	0.604	0.396	0.396
AC	544 (46.1)	379 (41.7)	0.86 (0.71,1.04)	197 (51.4)	128 (44.1)	0.69 (0.49,0.99)	0.132	0.116	0.955	0.948	0.955	0.484	0.484	245 (43.8)	164 (38.4)	0.86 (0.65,1.13)	0.042	0.110	0.250	0.250	0.250	0.250	0.398	0.671	15 (6.4)	15 (6.4)	1.19 (0.55,2.59)	0.662	0.664	0.581	0.581	0.573	0.604	0.707	0.664	0.707	0.604	0.396	0.396
AA	138 (11.7)	125 (13.7)	1.12 (0.86,1.50)	76 (19.9)	57 (19.7)	0.83 (0.53,1.29)	0.369	0.433	0.955	0.948	0.955	0.484	0.484	47 (8.4)	53 (12.4)	1.38 (0.89,2.15)	0.398	0.671	0.250	0.250	0.250	0.250	0.398	0.671	15 (6.4)	15 (6.4)	1.19 (0.55,2.59)	0.662	0.664	0.581	0.581	0.573	0.604	0.707	0.664	0.707	0.604	0.396	0.396
<i>TAS2R50</i> (rs1376251)																																							
TT	347 (29.6)	278 (30.6)	1.00 (reference)	224 (58.6)	161 (55.5)	1.00 (reference)	0.960	0.854	0.495	0.467	0.495	0.192	0.192	48 (8.6)	38 (8.9)	1.00 (reference)	0.795	0.725	0.684	0.684	0.684	0.684	0.795	0.725	75 (32.2)	79 (40.7)	1.00 (reference)	0.660	0.660	0.294	0.294	0.200	0.200	0.621	0.543	0.621	0.543	0.254	0.117
TC	518 (44.2)	405 (44.5)	0.98 (0.78,1.23)	139 (36.4)	110 (37.9)	1.15 (0.81,1.56)	0.960	0.854	0.495	0.467	0.495	0.192	0.192	253 (45.4)	209 (49.2)	1.07 (0.67,1.70)	0.795	0.725	0.684	0.684	0.684	0.684	0.795	0.725	126 (54.1)	86 (44.3)	0.66 (0.32,1.01)	0.660	0.660	0.294	0.294	0.200	0.200	0.621	0.543	0.621	0.543	0.254	0.117
CC	307 (26.2)	226 (24.9)	0.90 (0.68,1.19)	19 (5.0)	19 (6.6)	1.22 (0.62,2.40)	0.495	0.467	0.495	0.467	0.495	0.192	0.192	256 (46.0)	178 (41.9)	0.90 (0.56,1.44)	0.566	0.285	0.684	0.684	0.684	0.684	0.566	0.285	32 (13.7)	29 (15.0)	0.86 (0.47,1.57)	0.621	0.621	0.294	0.294	0.200	0.200	0.621	0.543	0.621	0.543	0.254	0.117

P-values for all odds ratios and 95% confidence intervals were partially-adjusted for race (where appropriate), age, sex, screening site, endoscopic procedure and additionally, fully-adjusted for family history of colorectal cancer, vitamin supplement use, years of education, smoking status, pack-years of cigarette smoking, lifetime physical activity, and body mass index.

[†]The *p* for interaction represents the significance of the gene-by-race/ethnicity interaction term from separate logistic regression analyses.

^{††}The *p* for trend is based on the score test for a variable assigned the dosage of the haplotype or variant allele