This is a repository copy of *Bitter taste sensitivity, food intake, and risk of malignant cancer in the UK Women's Cohort Study*.

Article:

1   Bitter taste sensitivity, food intake, and risk of malignant cancer in the UK Women's Cohort Study
2
3   Joshua D. Lambert[1,2,*], Sarah R. VanDusen[3], Jennie E. Cockroft[3], Elizabeth C. Smith[4], Darren C.
4   Greenwood[5], Janet E. Cade[3]
5   [1.] Department of Food Science and [2.] Center for Molecular Toxicology and Carcinogenesis, The
6   Pennsylvania State University, University Park, PA 16802 USA, [3.] Nutritional Epidemiology Group,
7   School of Food Science and Nutrition, [4.] School of Biology, Faculty of Biological Sciences, and [5.]
8   Biostatistics Unit, Faculty of Medicine and Health, University of Leeds, Leeds LS2 9JT, UK
9
10   **Running Title:** Bitter test sensitivity, food intake, and cancer
11
12
19
20   ***Corresponding Author:**
21   Joshua D. Lambert, PhD
22   Department of Food Science
23   Center for Molecular Toxicology and Carcinogenesis
24   The Pennsylvania State University
25   332 Food Science Building
26   University Park, PA 16802
27   USA
28   Email: jdl134@psu.edu
29   FAX: (814)863-6132
30   Tel: (814)865-5223
31
32   **Conflict of Interest Disclosure:** The authors have no conflicts of interest to disclose.
33
34
35   **Abbreviations:** BMI, body mass index; CI, 95% confidence interval; FFQ, food frequency
36   questionnaire; GI, gastrointestinal tract; HR, hazard ratio; OR, odds ratio; PROP, 6-propylthiouluracil;
37   PTC, phenylthiocarbamide; SES, socio-economic status; TAS2R38, taste 2 receptor 38; UKWCS,
38   United Kingdom Women's Cohort Study
39
40

ABSTRACT

Purpose: There is variability in sensitivity to bitter tastes. Taste 2 Receptor (TAS2R)38 binds to bitter tastants including phenylthiocarbamide (PTC). Many foods with putative cancer preventive activity have bitter tastes. We examined the relationship between PTC sensitivity or *TAS2R38* diplotype, food intake, and cancer risk in the UK Women's Cohort Study.

Methods: PTC taste phenotype (n = 5,500) and *TAS238* diplotype (n = 750) were determined in a subset of the cohort. Food intake was determined using a 217-item food frequency questionnaire. Cancer incidence was obtained from the National Health Service Central Register. Hazard ratios (HR) were estimated using multivariable Cox proportional hazard models.

Results: PTC tasters (HR = 1.30, 95% confidence interval [CI]: 1.04, 1.62), but not supertasters (HR = 0.98, CI: 0.76, 1.44), had increased cancer risk compared to nontasters. An interaction was found between phenotype and age for supertasters (p = 0.019) but not tasters (p = 0.54). Among women > 60 y, tasters (HR = 1.40 CI: 1.03, 1.90) and supertasters (HR = 1.58, CI: 1.06, 2.36) had increased cancer risk compared to nontasters, but no such association was observed among women ≤ 60 y (tasters HR = 1.16, CI: 0.84, 1.62; supertasters HR = 0.54, CI: 0.31, 0.94). We found no association between *TAS2R38* diplotype and cancer risk. We observed no major differences in bitter fruit and vegetable intake.

Conclusion: These results suggest that the relationship between PTC taster phenotype and cancer risk may be mediated by factors other than fruit and vegetable intake.

Keywords: bitter taste perception; cancer; food choice; epidemiology

2

INTRODUCTION

There is a strong and growing body of data to indicate that food and diet play a major role in the etiology and prevention of several types of cancer including breast, prostate, and gastrointestinal tract cancers (reviewed in [1-3]). The potential cancer preventive effects of fruits and vegetables have been attributed to the high fiber content, presence of bioactive phytochemicals, high levels of antioxidant vitamins, and/or low fat content of the food items [4]. By contrast, the putative cancer promoting effects of red and processed meats have been attributed to the presence of process-derived carcinogens, free heme iron, and/or saturated and oxidized fats [5].

Taste is critical driver of food choice and represents a potential complicating factor for effecting dietary changes to reduce cancer burden [6, 7]. Specifically, humans have an innate aversion to bitter tastes likely because these tastes have frequently indicated the presence of toxic or anti-nutritional compounds in plants [8]. A number of important dietary phytochemicals with putative cancer preventive activities including isothiocyanates have been reported to have strong bitter tastes [9-12]. Sensitivity to the bitter tastants is variable within a population, and the phenotypic and genotypic variability in bitter taste perception have been widely studied [6, 12].

Phenylthiocarbamide (PTC) is a chemical that mimics the bitter taste sensation of isothiocyanates from cruciferous vegetables, and is detectable in varying levels by different individuals [13, 14]. A derivative of PTC, 6-n-propylthiouricil (PROP), elicits a similar bitter taste response and is often used in place of PTC for taste studies. The spectrum of PTC/PROP sensitivity is very wide; some individuals will perceive an intense bitter taste comparable in magnitude to the brightest light imaginable (supertasters), others will taste nothing at all (nontasters), and most people will experience something in between (tasters) [15]. Supertasters, tasters, and nontasters differ not only in PTC/PROP sensitivity, but also in sensitivity to certain bitter foods.

The Taste 2 receptor 38 (TAS2R38) is one of 25 human TAS2Rs that function as bitter taste receptors in the taste buds of human papillae; TAS2R38 binds to isothiocyanates and several other classes of compounds [16-18]. Within the *TAS2R38* gene, 3 non-synonymous single nucleotide

3

90   polymorphisms (SNPs) give rise to the amino acid substitutions A49P ($A^{49} \rightarrow P^{49}$), A262V ($A^{262} \rightarrow V^{262}$),

91   and I296V ($I^{296} \rightarrow V^{296}$). These SNPs lead to five haplotypes that are responsible for varying levels of

92   phenotypic PTC/PROP sensitivity in humans. Because of a high level of linkage disequilibrium

93   between A262V and I296V, variation is seen only between A49P and A262V in practice [19]. The

94   PAV haplotype corresponds to a greater sensitivity to certain bitter tastes, whereas the AVI

95   haplotype corresponds to bitter taste insensitivity [19, 20].

96   Few studies have attempted to explore the relationship between bitter taste sensitivity, diet,

97   and cancer risk. Most of the existing literature has characterised PTC/PROP taster status and food

98   preferences, but did not actually test whether these preferences translate into differences in diet or

99   cancer risk [11, 13, 21]. A limited number of studies have examined the relationship between

100   *TAS2R38* diplotype, differences in diet, and risk of various cancers [22-26]. These studies have

101   yielded conflicting results regarding the impact of diplotype on risk. For example, a case-control

102   study of Korean adults (681 colorectal cancer cases, 1361 controls) reported that the subjects with

103   the AVI/AVI nontaster diplotype was associated with reduced risk of colorectal cancer (OR = 0.74,

104   95% confidence interval [CI]: 0.55, 0.98) compared to subjects with the PAV/PAV taster diplotype

105   [23]. Interestingly, there was no relationship between diplotype and fruit and vegetable, dietary

106   fiber, or energy intake. By contrast, a case-control study of German and Czech populations found

107   that subjects with the AVI/AVI diplotype had increased risk of colorectal cancer (OR = 1.33, CI: 1.03,

108   1.72) compared to subjects with PAV/PAV diplotype [25].

109   In the present study, we examined the association between bitter taste sensitivity (or

110   *TAS2R38* diplotype), food intake, and risk of malignant cancers using data derived from the UK

111   Women's Cohort Study (UKWCS). Our aims were to determine whether any association exists

112   between bitter taste phenotype (or *TAS2R38* diplotype), dietary patterns, and risk of developing

113   malignant cancer.

114

115   **METHODS**

Subject Population

The UKWCS was established to study the relationships between diet and diseases such as cancer in women in the UK [27]. Between 1995 and 1998, 35,372 women across England, Scotland, and Wales between the ages of 35 and 69 were recruited into the cohort. Other lifestyle characteristics were also recorded. The cohort was registered with the National Health Service Central Register to provide information on cancer incidence and deaths. The primary Taste Genetics (TaG I) Study, which contacted a sub-sample of 5500 women from the UKWCS, began in 2003. The women in the TaG I sub-sample were selected from the whole cohort based on their high response rates during each data collection point in the UKWCS. Respondents were categorised as nontasters, tasters, or supertasters based on their response to PTC-impregnated filter papers using a Labelled Magnitude Scale [28]. They were also asked to provide data regarding food preferences and food behaviours. Exclusion criteria included being currently pregnant or breast-feeding, history of otitis media, or taking medication that would alter the sense of smell or taste.

TAS2R38 SNP Status

Of the responders to TAG I, a random sample of 750 (20%) women were contacted one year later, re-tested for PTC taster status, and asked to provide a saliva sample for DNA collection from buccal cells. Samples were collected using Oragene DNA collection kits according to the manufacturer's protocol (DNA Genotek, Ottawa, Canada) and either immediately extracted by rapid alkaline lysis, or stored at 4°C prior to extraction when necessary. Real-time polymerization chain reaction (qPCR) was used for sequence analysis of three loci in *TAS2R38* containing SNPs (A145P, V262A, and I296V), which account for the 5 reported haplotypes of *TAS2R38*: AVI/AVI, AVI/AAV, AAV/PAV, AVI/PAV, and PAV/PAV [19]. TaqMan SNP assays were used for SNP analysis and qPCR was performed using an ABI9700HT Fast Real-Time System in the 384-well format (ThermoFisher Scientific, Waltham, MA, USA). SNP haplotypes were reconstructed from PCR result using PHASE

142 three most abundant haplotypes: PAV/PAV, PAV/AVI, and AVI/AVI.

143

144 **Baseline Characteristics and Dietary Information**

145 Age, height, and weight were self-reported at the time of TaG I study recruitment. If height or

146 weight data were missing from the TaG I data-set, then these values were imputed from the baseline

147 data-set. Body mass index (BMI) was calculated based on self-reported height (meters) and weight

148 (kg). Ethnicity, smoking status, menopausal status, and adoption of a vegan or vegetarian diet were

149 self-reported at baseline and are categorical or binary variables. Postmenopausal women included

150 women that self-reported undergoing hormone replacement therapy. Dietary data was collected at

151 baseline using a 217-item food frequency questionnaire (FFQ) that was previously validated using a

152 4-day food diary [27, 29]. Participant socio-economic status (SES) was categorized as:

153 managerial/professional, intermediate, routine/manual based occupation according to the United

154 Kingdom Statistics-Socio-Economic Classification [30]. Intake of specific food items were self-

155 reported in response to the question, "How often have you eaten these foods in the last 12

156 months?" and included 10 possible responses ranging from "never" to "6+ times per day". Nutrient

157 content of each food item were determined based on *The Composition of Foods* (5th Edition) [31].

158 Nutrient intakes were calculated by applying a standard portion size to each category and summing

159 the nutrient contribution of each food category to arrive at a total daily nutrient intake. Total fruit

160 and vegetable intake was calculated by summing daily intake of individual fruit (including dried

161 fruits) and vegetable (excluding potatoes) items. Total meat consumption represents the sum of

162 reported frequency of consumption of dishes made from beef, pork, lamb, chicken and other meats

163 including bacon and offal. Consumption of fruit and vegetables, red meat, and total meat are

164 expressed in grams per day (g/d).

165

166 **Incident Cancer**

167   Incident cancer information for the period from baseline to 4th April 2014 was obtained from the

168   National Health Service Central Register. Time since baseline was used in the survival analysis.

169

170   **Statistical Analysis**

171   Statistical analyses were carried out using Stata, version 15 (Stata Corp., LLC, College Station, TX,

172   USA). The characteristics of the women in the sample were compared across PTC taster phenotype

173   and diplotype using regression analysis for continuous variables and χ-squared tests for categorical

174   data. The TaG I questionnaire included a section assessing the degree to which an individual liked

175   various foods by asking whether they had "never tried", "like extremely", "like a lot", "like", "like a

176   little", "neither like nor dislike", " dislike a little", "dislike", "dislike a lot", or "dislike extremely" to

177   each of 217 foods. These responses were simplified to: "never tried", "like", "neither like nor

178   dislike", or "dislike". The mean number of "likes", "dislikes", and "never trieds" were compared

179   between PTC taster status groups. All continuous variables are presented as the geometric means

180   with 95% confidence intervals (CI).

181   Differences in consumption of select fruits and vegetables, total vegetables, total fruits, red

182   meat, and total meat in grams per day across PTC taster status groups and *TAS2R38* diplotypes were

183   assessed using regression analysis. These foods were included based on known bitter taste profiles,

184   content of known bitter phytochemicals, or a relationship to cancer incidence. It was decided not to

185   include coleslaw and low-calorie coleslaw as the fat content might mask the bitterness of the

186   cabbage [32]. Supertasters may also perceive the creaminess as less appealing [33]. Prior to

187   analysis, all foods were transformed using the following formula (y = log (reported intake [in grams

188   per day] + 0.01 g)), to account for the large number of non-consumers of any one food item. The

189   procedure above was repeated for phenotypic and genotypic differences between major

190   macronutrients and micronutrients. Risk of developing any malignant cancer according to bitter

191   taste phenotype or *TAS2R38* diplotype was estimated using Cox proportional hazards models to

192   calculate a hazard ratio (HR) and CI. Person-years were calculated from the date the baseline

7

193   questionnaire was completed until the first occurrence of either a report of any incident cancer,

194   death or the censor date of the analysis (4th April 2014). Associations were estimated first using a

195   simple unadjusted model, and then using a model that included age, BMI, and smoking status as

196   potential confounders. The interaction between phenotype and age was also examined given the

197   reported impact of age on bitter taste sensitivity [34, 35]. Interactions between covariates and taster

198   phenotype were examined and the Likelihood ratio test was performed to provide statistical

199   evidence for inclusion/exclusion of the interaction terms in the final model.

200

201   **Ethical Approval**

202   One hundred and seventy-four local research ethics committees were contacted and permission to

203   carry out the baseline study was obtained [27]. Further approval for collecting diplotype and

204   phenotype data was granted by the Multiple Research Ethics Committee (Ref 03/10/316).

205

206   **RESULTS**

207   **Baseline Characteristics**

208   A total of 3,328 women were included in the final analysis. Women were excluded from the final

209   data-set if they had extreme BMI (< 16 kg/m^2 or > 50 kg/m^2), extreme daily energy intake (< 500

210   kcal/d or > 6,000 kcal/d), or unreasonable total fruit and vegetable intake (> 3,000 g/d). Baseline

211   characteristics of the subjects are shown *in toto* and separated based on bitter taster phenotype in

212   Table 1. Supertasters were significantly younger and included a slightly lower percentage of whites

213   and higher percentage of women of Indian/Pakistani origin, although this population represents a

214   small number of individuals in this cohort. Tasters included a higher percentage of premenopausal

215   women. There were no other significant differences in the baseline.

216

217   **Food and Nutrient Intake Across Phenotype and Diplotype**

8

218   Analysis of intake of specific bitter fruit and vegetables, tea, coffee, red meat and total meat across

219   phenotype (Table 2) showed that there was a small but statistically significant association between

220   phenotype and intake of cress vegetables: mean consumption was 0.62 g/d (CI: 0.58, 0.67), 0.63 (CI:

221   0.59, 0.67), and 0.61 (CI: 0.54, 0.67) for nontasters, tasters, and supertasters, respectively. There

222   was no evidence of association between taster phenotype and intake of other food items. No

223   significant associations were observed between the major *TAS2R38* diplotypes and intake of

224   particular food items (Table 2). No evidence of significant association was observed between

225   phenotype or diplotype and intake of total energy or the macro- and micronutrients examined

226   (Table 2).

227

228   **Survival Analysis**

229   HR and CI for the development of any malignant cancer were estimated across bitter taster

230   phenotype and *TAS2R38* diplotype (Table 3). After adjustment for age, BMI, and smoking status,

231   tasters had a 28% greater risk for malignant cancer incidence (HR = 1.28, CI: 1.03, 1.60) compared to

232   nontasters (Table 3). No evidence of association was observed between the supertaster phenotype

233   and cancer incidence (HR = 1.05, CI: 0.76, 1.44). No significant association was observed between

234   *TAS2R38* diplotype and malignant cancer incidence in either model (Table 3). Age was identified as a

235   significant covariate in the overall survival analysis ($p < 0.001$). We stratified women into two age

236   groups (≤ 60 [n = 1,992] vs. > 60 y old [n = 1,343]) and examined the interaction between phenotype

237   and age group. A significant interaction was observed between phenotype and age among

238   supertasters ($p = 0.019$) but not for tasters ($p = 0.541$). Likelihood ratio test showed that inclusion of

239   the interaction term improves model fit ($p = 0.015$). Survival analysis for the main effect of

240   phenotype on malignant cancer risk was performed for each age group. No evidence of association

241   was observed between phenotype and malignant cancer incidence in younger women with the

242   taster phenotype (Table 4). By contrast, younger women with the supertaster phenotype had a

243   lower risk of malignant cancer (fully adjusted HR = 0.54, CI: 0.31, 0.94) compared to women with the

9

244   nontaster phenotype (Table 4). Analysis of older women showed that tasters (HR = 1.40, CI: 1.03,

245   2.90) and supertasters (HR = 1.58, CI: 1.06, 2.36) had higher risk of malignant cancer incidence

246   compared to nontasters (Table 4).

247

248   **Age-Stratified Dietary Characteristics**

249   Given differences observed in the survival analysis after stratifying for age, we stratified the food

250   intake data by age and compared intake across bitter taster phenotype. In the younger women, the

251   only significant association was between cress vegetables and phenotype (Suppl. Table 1). Mean

252   intake of cress vegetables was 0.61 g/d (CI: 0.56, 0.68), 0.58 (CI: 0.53, 0.63), and 0.62 (CI: 0.54, 0.71)

253   for nontasters, tasters, and supertasters, respectively. In older women, there was a positive

254   association between phenotype and red meat intake (p = 0.039); supertasters (38.4 g/d, CI: 33.6,

255   43.8) and tasters (35.5 g/d, CI: 32.8, 38.4) had a greater mean intake of red meat than nontasters

256   (33.6 g/d, CI: 29.9, 37.9). We also examined the relationship between bitter taster phenotype and

257   intake of food ingredients that may impact bitter perception: carbohydrates, fat, and salt. In

258   younger women, but not older women, there was a significant, positive association between bitter

259   taster phenotype and total carbohydrate and sugar intake (Suppl. Table 2). Among supertasters,

260   mean intake of total carbohydrates and sugar were 313.6 g/d (CI: 302.5, 325.1) and 145.1 g/d (CI:

261   139.1, 151.3), respectively. By contrast, mean consumption of total carbohydrates and sugar among

262   nontasters were 302.5 g/d (CI: 295.7, 309.6) and 138.0 g/d (CI: 134.2, 142.0).

263

264   **DISCUSSION**

265   In the present study, we examined the relationship between bitter taster phenotype or *TAS2R38*

266   diplotype, food intake, and risk of incident malignant cancer in a population of British women. We

267   hypothesized that women with the taster and supertaster phenotype, or *TAS2R38* PAV/* diplotype,

268   would have reduced bitter fruit and vegetable intake, reduced total fruit and vegetable intake, and

269   an increased risk of incident malignant cancer compared to women with the nontaster phenotype or

270 diplotype. We found that tasters had higher risk of incident malignant cancer compared to

271 nontasters. Age was a significant covariate for malignant cancer risk and we observed a significant

272 interaction between bitter taste phenotype and age for supertasters, but not nontasters or tasters.

273 For this reason, sub-group analysis was performed (≤ 60 vs. > 60 y old). This analysis showed that in

274 women over 60 y old, those with either the taster phenotype or the supertaster phenotype were at

275 greater risk of incident malignant cancer than women with the nontaster phenotype. This observed

276 relationship in women 60 y old and younger was different. In this sub-group, there was no

277 association between the taster phenotype and cancer risk, whereas women with the supertaster

278 phenotype had lower risk of incident malignant cancer. The number of supertasters in the cohort

279 was relatively small (n = 507 subjects and n = 51 cases) and the CI wide.

280   The reasons for different relationships between phenotype and cancer risk between the age

281 groups and the observed decrease in cancer risk among supertasters are unclear. Examination of

282 the types of cancer prevalent in both the older and younger populations show that

283 reproductive/hormone-related cancers, GI cancers, and skin cancers were the most common

284 malignancies, and that the differential risk between older and younger women is driven primarily by

285 differences in reproductive/hormone-related cancers (Suppl. Fig. 1). This could indicate an

286 unidentified interactions between drivers of bitter taste sensitivity and estrogen signalling.

287 Alternatively, the decreased cancer risk could be the result of chance due to the low number of

288 incident cancer cases among younger women with the supertaster phenotype (n = 51 cases).

289 Further studies with larger populations of known PTC status, and larger numbers of incident cancer

290 cases, are needed to better test the veracity of the observed relationship with phenotype.

291   We also examined the relationship between the three most common *TAS2R38* diplotypes,

292 food intake, and risk of incident malignant cancer. We found no evidence of a significant

293 relationship between diplotype and cancer risk. It is unclear how generalizable this lack of

294 association is given the small number of subjects and cancer cases, and the large confidence

11

295   intervals of the HR estimates. Previous studies have yielded mixed results with regard to the impact

296   of *TAS2R38* diplotype [22-26].

297   Overall analysis of the relationship between food and nutrient intake and phenotype

298   revealed few differences. We observed no significant association between taste phenotype and

299   total fruit and vegetable intake, intake of specific bitter fruits and vegetables, or intake of different

300   macro- and micronutrients. The only exception was a small but significant association between

301   intake of cress vegetables and phenotype with supertasters having slightly lower intake of cress

302   vegetables than nontasters. Sub-group analysis showed that tasters and supertasters in the older

303   age sub-group had higher mean red meat intake compared to women with the nontaster

304   phenotype. No other significant differences were observed in this sub-group. Within the younger

305   sub-group, mean cress vegetable intake, mean total carbohydrate intake, and mean sugar intake

306   were positively associated with phenotype. We observed no significant relationship between

307   diplotype and food intake patterns. The lack of clear relationship between bitter taste phenotype

308   and mean intake of these foods observed in this study does not support the popular hypothesis that

309   tasters and supertasters will consume fewer vegetables and therefore be at increased risk for

310   developing malignant cancers.

311   The existing literature for the relationship between PROP/PTC status and fruit and vegetable

312   preference and intake is limited and conflicted [36-39]. One study examined the relationship

313   between PROP taster status and food preferences in a small cohort (n = 170) newly diagnosed breast

314   cancer patients who had not yet undergone radiation or chemotherapy, and found that women with

315   the taster and supertaster phenotype gave lower food preferences scores for "cruciferous

316   vegetables", "green vegetables", and "vegetables" [39]. These investigators did not, however,

317   assess intake in this population. Similarly, a cohort study of young children (aged 4 – 6 years) in the

318   New York City area found that children with the taster phenotype who lived in "healthy food

319   environments" had decreased liking scores for vegetables than children with the nontaster

320   phenotype [37]. By contrast, in a study of 120 Japanese children, there was no association between

321   PROP status and vegetable intake [36]. Yackinous and Guinard investigated the relationship PROP

322   status and dietary intake in a cohort of American college students (n = 183), and reported that, with

323   the exception of green salads and fruit, there was no significant effect of phenotype on fruit and

324   vegetable intake in women [40]. No relationship was observed in men.

325   The lack of evident association between diet and bitter taste sensitivity suggests that other

326   factors are more important in making individual food choices. Cultural and age differences have also

327   been found to influence food choice and preference [13]. Navarro-Allende et al., proposed that

328   genetic haplotypes may be less able to predict diets in more elderly people as neophobia and loss of

329   taste sensitivity with age may both be factors [41]. Furthermore, this sample consists of a low

330   number of smokers and a high number of affluent women. The factors most important in motivating

331   food choice in women with high fruit and vegetable intakes in the UKWCS were found to be health

332   and natural content of the food [42]. The women in this analysis are amongst the highest fruit and

333   vegetable consumers and may not be representative of the average women in the UK in terms of

334   factors affecting dietary choices.

335   Studies on the relationship between *TAS2R38* diplotype and diet within the context of

336   cancer have also failed to observe a relationship between diplotype and fruit and vegetable intake

337   [22-26]. Given the large number of TAS2R family members and the differences in their ligand

338   specificity, it is possible that selection of a different TAS2R family member might yield different

339   results. Further study with larger numbers of subjects and a more comprehensive approach to

340   TAS2R diplotype is needed to better understand the impact of bitter taste receptor genotype, food

341   intake, and cancer risk.

342   Interestingly, we did observe in the present analysis that older women with the taster

343   phenotype (5.3% higher) and supertaster phenotype (12.5% higher) had higher mean intake of red

344   meat than women in the nontaster phenotype. It is unclear why tasters and supertasters would

345   consume more red meat than nontasters, but this finding is provocative given the growing body of

346   data which shows that red meat intake is positively correlated with risk of total incident cancers as

347　well as incident breast cancer [5, 43-45]. This difference in red meat intake patterns may play a role

348　in the differences in incident malignant cancer risk in older versus younger women, but this result

349　requires confirmation by other large cohort studies.

350　　Our study has several limitations which must be considered. First, the number of cancer

351　cases in each phenotype is relatively small especially for the supertaster phenotype. Similarly, the

352　number of subjects genotyped for *TAS2R38* SNPs was relatively small, and the number of cancer

353　cases in this subset of the study population was very low (~50 cases). These low numbers of cases

354　limited the power of sub-analyses and precluded an effective analysis of risk for specific cancers.

355　Food intake data in the present study is self-reported. There is therefore the potential for over-

356　reporting intake of "healthy" foods and under-reporting intake of "unhealthy" foods as has been

357　noted as a potential confounder for FFQs [46, 47]. Height, body weight, and smoking status were

358　also self-reported and therefore susceptible to inaccuracy in reporting. In addition, both body

359　weight and smoking status may have changed between measurement at baseline and cancer

360　diagnosis. Finally, we confined SNP analysis in the present study to differences in *TAS2R38*.

361　Although TAS2R38 is an important member of the TAS2R family and is primarily responsible for

362　differences in PTC/PROP status, it is not the only predictor of liking of bitter foods [16, 48-50].

363　Moreover, there has been some discussion more recently that supertasters are a group of people

364　who are more sensitive not just to bitter taste, but to spiciness, sweetness, and other food textural

365　cues, owing to a greater number of fungiform papillae on their tongues [51, 52]. This increased

366　number of fungiform papillae is independent of TAS2R38 SNPs although their expression may be

367　controlled by the same family of receptors [53]. In order to better identify supertasters in this

368　sample, it would have been ideal to also assess fungiform papillae but such an assessment would

369　have proven difficult.

370　　Our study has several strengths compared to previous investigations into the relationship

371　between bitter sensitivity, food intake, and cancer risk. The UKWCS is a large prospective cohort

372　study that has included a long follow-up period. The study includes data on a wide variety of diet

14

373   and health-related markers, which facilitates careful examination of questions focused on diet and

374   chronic disease. The study is the largest of its kind to investigate the relationship between PTC

375   taster status, food intake, and cancer risk. In addition, we have, for the first time, examined both

376   bitter taster phenotype and *TAS2R38* diplotype and risk of cancer in the same population.

377   In summary, we report that PTC taster status is positively associated with risk of incident

378   malignant cancer in women over 60 years old. This increased risk was not associated with changes

379   in fruit and vegetable intake, but was associated with mean intake of red meat consumption.

380   Conversely, among women 60 years old and younger, women with the PTC supertaster phenotype

381   had significantly reduced cancer risk. We found no significant association between *TAS2R38*

382   diplotype and food intake patterns, or cancer risk. These results indicate that the relationship

383   between PTC taster status, food intake, and cancer risk is complex and indicates that future studies

384   on this relationship need to examine relevant endpoints for each aspect of the relationship rather

385   than extrapolate changes in one factor based on the changes in another.

386

387   **Conflict of Interest Disclosure:** The authors have no conflicts of interest to disclose.

388

REFERENCES

389

390 1. Lund EK, Belshaw NJ, Elliott GO, Johnson IT (2011) Recent advances in understanding the

391 role of diet and obesity in the development of colorectal cancer. Proc Nutr Soc 70:194-204.

392 2. Kerr J, Anderson C, Lippman SM (2017) Physical activity, sedentary behaviour, diet, and

393 cancer: an update and emerging new evidence. Lancet Oncol 18:e457-e471.

394 3. Turati F, Rossi M, Pelucchi C, Levi F, La Vecchia C (2015) Fruit and vegetables and cancer risk:

395 a review of southern European studies. Br J Nutr 113 Suppl 2:S102-110.

396 4. Rodriguez-Casado A (2016) The Health Potential of Fruits and Vegetables Phytochemicals:

397 Notable Examples. Crit Rev Food Sci Nutr 56:1097-1107.

398 5. Domingo JL, Nadal M (2017) Carcinogenicity of consumption of red meat and processed

399 meat: A review of scientific news since the IARC decision. Food Chem Toxicol 105:256-261.

400 6. Feeney E, O'Brien S, Scannell A, Markey A, Gibney ER (2011) Genetic variation in taste

401 perception: does it have a role in healthy eating? Proc Nutr Soc 70:135-143.

402 7. Glanz K, Basil M, Maibach E, Goldberg J, Snyder D (1998) Why Americans eat what they do:

403 taste, nutrition, cost, convenience, and weight control concerns as influences on food

404 consumption. J Am Diet Assoc 98:1118-1126.

405 8. des Gachons CP, Beauchamp GK, Breslin PAS (2009) The Genetics of Bitterness and Pungency

406 Detection and Its Impact on Phytonutrient Evaluation. In: Finger TE (ed) International

407 Symposium on Olfaction and Taste. p 140-144

408 9. Drewnowski A, Gomez-Carneros C (2000) Bitter taste, phytonutrients, and the consumer: a

409 review. Am J Clin Nutr 72:1424-1435.

410 10. Basson MD, Bartoshuk LM, Dichello SZ, Panzini L, Weiffenbach JM, Duffy VB (2005)

411 Association between 6-n-propylthiouracil (PROP) bitterness and colonic neoplasms. Dig Dis

412 Sci 50:483-489.

413 11. Akella GD, Henderson SA, Drewnowski A (1997) Sensory acceptance of Japanese green tea

414   and soy products is linked to genetic sensitivity to 6-n-propylthiouracil. Nutr Cancer 29:146-

415   151.

416 12. Hansen JL, Reed DR, Wright MJ, Martin NG, Breslin PA (2006) Heritability and genetic

417   covariation of sensitivity to PROP, SOA, quinine HCl, and caffeine. Chem Senses 31:403-413.

418 13. Drewnowski A (1997) Taste preferences and food intake. Annu Rev Nutr 17:237-253.

419 14. Drewnowski A, Henderson SA, Shore AB (1997) Taste responses to naringin, a flavonoid, and

420   the acceptance of grapefruit juice are related to genetic sensitivity to 6-n-propylthiouracil.

421   Am J Clin Nutr 66:391-397.

422 15. Lucchina LA, Curtis VOF, Putnam P, Drewnowski A, Prutkin JM, Bartoshuk LM (1998)

423   Psychophysical measurement of 6-n-propylthiouracil (PROP) taste perception. Ann NY Acad

424   Sci 855:816-819.

425 16. Chandrashekar J, Mueller KL, Hoon MA, Adler E, Feng L, Guo W, Zuker CS, Ryba NJ (2000)

426   T2Rs function as bitter taste receptors. Cell 100:703-711.

427 17. Andres-Barquin PJ, Conte C (2004) Molecular basis of bitter taste: the T2R family of G

428   protein-coupled receptors. Cell Biochem Biophys 41:99-112.

429 18. Meyerhof W, Batram C, Kuhn C, Brockhoff A, Chudoba E, Bufe B, Appendino G, Behrens M

430   (2010) The molecular receptive ranges of human TAS2R bitter taste receptors. Chem Senses

431   35:157-170.

432 19. Kim U-k, Jorgenson E, Coon H, Leppert M, Risch N, Drayna D (2003) Positional Cloning of the

433   Human Quantitative Trait Locus Underlying Taste Sensitivity to Phenylthiocarbamide.

434   Science 299:1221-1225.

435 20. Drewnowski A, Rock CL (1995) The influence of genetic taste markers on food acceptance.

436   Am J Clin Nutr 62:506-511.

437 21. Dinehart ME, Hayes JE, Bartoshuk LM, Lanier SL, Duffy VB (2006) Bitter taste markers explain

438   variability in vegetable sweetness, bitterness, and intake. Physiol Behav 87:304-313.

439 22. Yamaki M, Saito H, Isono K, Goto T, Shirakawa H, Shoji N, Satoh-Kuriwada S, Sasano T, Okada

440   R, Kudoh K, Motoi F, Unno M, Komai M (2017) Genotyping Analysis of Bitter-Taste Receptor

441   Genes TAS2R38 and TAS2R46 in Japanese Patients with Gastrointestinal Cancers. J Nutr Sci

442   Vitaminol (Tokyo) 63:148-154.

443 23. Choi JH, Lee J, Oh JH, Chang HJ, Sohn DK, Shin A, Kim J (2017) Variations in the bitterness

444   perception-related genes TAS2R38 and CA6 modify the risk for colorectal cancer in Koreans.

445   Oncotarget 8:21253-21265.

446 24. Choi JH, Lee J, Choi IJ, Kim YW, Ryu KW, Kim J (2016) Genetic Variation in the TAS2R38 Bitter

447   Taste Receptor and Gastric Cancer Risk in Koreans. Sci Rep 6:26904.

448 25. Carrai M, Steinke V, Vodicka P, Pardini B, Rahner N, Holinski-Feder E, Morak M, Schackert

449   HK, Gorgens H, Stemmler S, Betz B, Kloor M, Engel C, Buttner R, Naccarati A, Vodickova L,

450   Novotny J, Stein A, Hemminki K, Propping P, Forsti A, Canzian F, Barale R, Campa D (2011)

451   Association between TAS2R38 gene polymorphisms and colorectal cancer risk: a case-

452   control study in two independent populations of Caucasian origin. PLoS One 6:e20464.

453 26. Schembre SM, Cheng I, Wilkens LR, Albright CL, Marchand le L (2013) Variations in bitter-

454   taste receptor genes, dietary intake, and colorectal adenoma risk. Nutr Cancer 65:982-990.

455 27. Cade J, Burley V, Greenwood D (2004) The UK Women's Cohort Study: comparison of

456   vegetarians, fish-eaters and meat-eaters. Public Health Nutr 7:871-878.

457 28. Green BG, Dalton P, Cowart B, Shaffer G, Rankin K, Higgins J (1996) Evaluating the 'Labeled

458   Magnitude Scale' for measuring sensations of taste and smell. Chem Senses 21:323-334.

459 29. Spence M, Cade JE, Burley VJ, Greenwood DC (2002) Ability of the UK Women's Cohort Food

460   Frequency Questionnaire to rank dietary intakes: a preliminary validation study. Proc Nutr

461   Soc 61:117A.

462 30. Rose D, Pevalin D, O'Reilly K (2005) The national statistics socio-economic classification:

463   origins, development and use. Palgrave Macmillan, Hampshire

464   31.   Holland B, Welch AA, Unwin ID, Buss DH, Paul AA, Southgate DAT (1991) McCance &

465   Widdowson's The composition of foods. Royal Society of Chemistry and Ministry of

466   Agriculture, Fisheries, and Food, London

467   32.   Ly A, Drewnowski A (2001) PROP (6-n-Propylthiouracil) tasting and sensory responses to

468   caffeine,sucrose, neohesperidin dihydrochalcone and chocolate. Chem Senses 26:41-47.

469   33.   Tepper BJ, Nurse RJ (1998) PROP taster status is related to fat perception and preference.

470   Ann NY Acad Sc 855:802-804.

471   34.   Methven L, Allen VJ, Withers CA, Gosney MA (2012) Ageing and taste. Proc Nutr Soc 71:556-

472   565.

473   35.   Koskinen S, Kalviainen N, Tuorila H (2003) Perception of chemosensory stimuli and related

474   responses to flavored yogurts in the young and elderly. Food Quality and Preference 14:623-

475   635.

476   36.   Tsuji M, Nakamura K, Tamai Y, Wada K, Sahashi Y, Watanabe K, Ohtsuchi S, Ando K, Nagata C

477   (2012) Relationship of intake of plant-based foods with 6-n-propylthiouracil sensitivity and

478   food neophobia in Japanese preschool children. Eur J Clin Nutr 66:47-52.

479   37.   Burd C, Senerat A, Chambers E, Keller KL (2013) PROP taster status interacts with the built

480   environment to influence children's food acceptance and body weight status. Obesity (Silver

481   Spring) 21:786-794.

482   38.   Ullrich NV, Touger-Decker R, O'Sullivan-Maillet J, Tepper BJ (2004) PROP taster status and

483   self-perceived food adventurousness influence food preferences. J Am Diet Assoc 104:543-

484   549.

485   39.   Drewnowski A, Henderson SA, Hann CS, Berg WA, Ruffin MT (2000) Genetic taste markers

486   and preferences for vegetables and fruit of female breast care patients. J Am Diet Assoc

487   100:191-197.

488 40. Yackinous CA, Guinard JX (2002) Relation between PROP (6-n-propylthiouracil) taster status,

489   taste anatomy and dietary intake measures for young men and women. Appetite 38:201-

490   209.

491 41. Navarro-Allende A, Khataan N, El-Sohemy A (2008) Impact of genetic and environmental

492   determinants of taste with food preferences in older adults. J Nutr Elder 27:267-276.

493 42. Pollard J, Greenwood D, Kirk S, Cade J (2002) Motivations for fruit and vegetable

494   consumption in the UK Women's Cohort Study. Public Health Nutr 5:479-486.

495 43. Diallo A, Deschasaux M, Latino-Martel P, Hercberg S, Galan P, Fassier P, Alles B, Gueraud F,

496   Pierre FH, Touvier M (2017) Red and processed meat intake and cancer risk: Results from the

497   prospective NutriNet-Sante cohort study. Int J Cancer.

498 44. Wu J, Zeng R, Huang J, Li X, Zhang J, Ho JC, Zheng Y (2016) Dietary Protein Sources and

499   Incidence of Breast Cancer: A Dose-Response Meta-Analysis of Prospective Studies.

500   Nutrients 8.

501 45. Guo J, Wei W, Zhan L (2015) Red and processed meat intake and risk of breast cancer: a

502   meta-analysis of prospective studies. Breast Cancer Res Treat 151:191-198.

503 46. Cade JE, Burley VJ, Warm DL, Thompson RL, Margetts BM (2004) Food-frequency

504   questionnaires: a review of their design, validation and utilisation. Nutr Res Rev 17:5-22.

505 47. Brunner E, Stallone D, Juneja M, Bingham S, Marmot M (2001) Dietary assessment in

506   Whitehall II: comparison of 7 d diet diary and food-frequency questionnaire and validity

507   against biomarkers. Br J Nutr 86:405-414.

508 48. Wooding S, Gunn H, Ramos P, Thalmann S, Xing C, Meyerhof W (2010) Genetics and bitter

509   taste responses to goitrin, a plant toxin found in vegetables. Chem Senses 35:685-692.

510 49. Hayes JE, Bartoshuk LM, Kidd JR, Duffy VB (2008) Supertasting and PROP bitterness depends

511   on more than the TAS2R38 gene. Chem Senses 33:255-265.

512   50.   Hayes JE, Wallace MR, Knopik VS, Herbstman DM, Bartoshuk LM, Duffy VB (2011) Allelic

513   variation in TAS2R bitter receptor genes associates with variation in sensations from and

514   ingestive behaviors toward common bitter beverages in adults. Chem Senses 36:311-319.

515   51.   Bartoshuk LM, Duffy VB, Miller IJ (1994) PTC/PROP tasting: anatomy, psychophysics, and sex

516   effects. Physiol Behav 56:1165-1171.

517   52.   Snyder DJ, Duffy VB, Marino SE, Bartoshuk LM (2008) We are what we eat, but why?

518   Relationships between oral sensation, genetics, pathology, and diet. In: Weerasinghe DK,

519   DuBois GE (eds) Sweetness and Sweeteners - Biology, Chemistry, and Psychophysics. Oxford

520   University Press, Oxford, p 258 - 284

521   53.   Behrens M, Foerster S, Staehler F, Raguse JD, Meyerhof W (2007) Gustatory expression

522   pattern of the human TAS2R bitter receptor gene family reveals a heterogenous population

523   of bitter responsive taste receptor cells. J Neurosci 27:12630-12640.

524

525

Table 1. Subject characteristics by PTC taster status

	Nontaster N = 1,084	Taster N = 1,714	Supertaster N = 530	Total N = 3,328	P-value[*]
Age (y), mean (95%CI)	58.2 (57.7, 58.7)	58.4 (58.0, 58.8)	56.9 (56.3, 57.6)	58.1 (57.8, 58.4)	0.040
BMI (Kg/m^2), mean (95%CI)	24.0 (23.8, 24.2)	23.7 (23.6, 23.9)	24.2 (23.9, 24.5)	23.9 (23.8, 24.0)	0.744
Current Smoker n (%)	30 (3)	47 (3)	17 (3)	92 (3)	0.807
Post-menopausal n (%)	51 (541)	916 (53)	249 (46)	1,710 (51)	0.011
Socioeconomic Status n (%)					0.356
Professional/Managerial	735 (69)	1,141 (67)	64 (343)	2,217 (67)	
Intermediate	260 (24)	446 (26)	28 (151)	860 (26)	
Routine/Manual	70 (7)	119 (7)	8 (41)	232 (7)	
Ethnic group n (%)					0.036
White	1,064 (99.4)	1,658 (99.3)	525 (98.3)	3,277 (99.2)	
Indian	3 (0.3)	5 (0.2)	6 (1.1)	13 (0.4)	
Other	3 (0.3)	2 (0.5)	3 (0.6)	13 (0.4)	
Food preferences, mean (95%CI)					
Likes (no. of foods)	152 (150, 154)	153 (152, 155)	150 (147, 152)	152 (151, 153)	0.395
Dislikes (no. of foods)	36 (35, 37)	35 (34, 36)	38 (36, 40)	36 (35, 36)	0.106
Never Tried (no. of foods)	9 (9, 10)	9 (9, 10)	9 (9, 10)	9 (9, 10)	0.646
Diplotype n (%)					< 0.001
AVI/AVI	131 (91.1)	11 (5.1)	1 (1.3)	144 (32.5)	
AVI/PAV	12 (8.3)	161 (73.8)	50 (64.9)	224 (50.6)	
PAV/PAV	1 (0.7)	46 (21.1)	26 (33.8)	75 (16.9)	

[*] Continuous variables were analysed by regression analysis. Categorical variables were analysed by Pearson's χ^2.

Table 2. Selected food and nutrient intake by PTC taster status and *TAS2R38* diplotype

		Taster Status				P-value[*]
		Nontaster	Taster	Supertaster	Total	
Food Item		Mean Intake gram/d (95%CI)[**]				
Broccoli, spring greens, kale		17.3 (16.4, 18.6)	17.1 (16.4, 17.9)	16.6 (15.3, 17.9)	17.1 (16.5, 17.6)	0.124
Brussel Sprouts		8.1 (7.6, 8.7)	8.1 (7.7, 8.5)	8.1 (7.4, 8.9)	8.1 (7.8, 8.4)	0.337
Cabbage		10.9 (10.2, 11.6)	10.4 (9.9, 10.9)	11.0 (10.1, 11.9)	10.6 (10.3, 11.0)	0.344
Cauliflower		12.9 (12.2, 13.6)	12.8 (12.3, 13.3)	13.3 (12.3, 14.4)	12.9 (12.5, 13.3)	0.548
Turnip		3.4 (3.1, 3.6)	3.4 (3.2, 3.6)	3.7 (3.3, 4.1)	3.4 (3.3, 3.5)	0.848
Cress vegetables		0.62 (0.58, 0.67)	0.63 (0.59, 0.67)	0.61 (0.54, 0.67)	0.62 (0.60, 0.65)	0.005
Oranges, grapefruits, etc.		22.4 (20.6, 24.4)	22.0 (20.6, 23.4)	22.3 (19.7, 25.2)	22.2 (21.2, 23.3)	0.899
Total Vegetables		251.4 (243.7, 259.3)	244.5 (238.5, 250.7)	254.1 (243.1, 265.7)	248.1 (243.7, 252.5)	0.969
Total Fruit		258.7 (248.0, 269.8)	256.1 (247.8, 264.7)	260.9 (245.1, 277.9)	258.0 (251.9, 264.2)	0.926
Total Fruit and Vegetables		539.8 (524.1, 556.0)	529.2 (517.1, 541.6)	548.0 (524.7, 572.3)	535.7 (526.9, 544.7)	0.843
Red Meat		34.2 (31.8, 36.7)	35.7 (33.8, 37.7)	35.5 (32.4, 39.0)	35.3 (33.9, 36.7)	0.061
Total Meat		60.8 (56.7, 65.3)	63.9 (60.6, 67.4)	72.2 (66.6, 78.1)	64.2 (61.8, 66.7)	0.335
Tea		431.9 (394.0, 473.4)	529.2 (496.7, 563.7)	484.2 (426.2, 550.2)	488.1 (465.0, 512.5)	0.931
Coffee		239.2 (218.0, 262.6)	244.8 (228.5, 262.3)	224.4 (196.5, 256.3)	239.7 (227.8, 252.2)	0.456
Nutrient						
Total Energy (kcal)		2222 (2184, 2261)	2210 (2179, 2242)	2263 (2203, 2325)	2223 (2200, 2245)	0.258
Protein (g/d)		85.9 (84.4, 87.4)	85.9 (84.7, 87.2)	86.8 (84.5, 89.1)	86.1 (85.2, 86.9)	0.465
Carbohydrates (g/d)	Total	303.8 (298.3, 309.5)	301.0 (296.5, 305.5)	309.0 (300.2, 318.1)	303.2 (300.0, 306.5)	0.268
	Starch	147.8 (144.7, 151.0)	145.3 (142.8, 147.8)	148.2 (143.4, 153.2)	146.6 (144.8, 148.4)	0.834
	Sugar	141.9 (138.7, 145.1)	142.2 (139.7, 144.8)	146.4 (141.6, 151.5)	142.0 (140.9, 144.7)	0.082
	Fibre	25.0 (24.4, 25.5)	24.4 (23.9, 24.8)	24.9 (24.1, 25.8)	24.7 (24.3, 25.0)	0.883
Fat (g/d)	Total	80.2 (78.5, 82.0)	79.9 (78.4, 81.3)	82.1 (79.5, 84.8)	80.3 (79.3, 81.4)	0.297
	Saturated	26.6 (25.9, 27.3)	26.7 (26.2, 27.3)	27.7 (26.7, 28.7)	26.8 (26.4, 27.2)	0.176
	MUFA	26.1 (25.5, 26.7)	25.9 (25.5, 26.4)	26.7 (25.8, 27.6)	26.1 (25.7, 26.5)	0.342
	PUFA	15.5 (15.2, 15.9)	15.2 (14.9, 15.5)	15.7 (15.2, 16.3)	15.4 (15.2, 15.6)	0.406
Vitamins	Vit. C (mg/d)	162.6 (158.5, 166.9)	159.7 (156.4, 163.1)	165.0 (158.5, 171.6)	161.5 (159.1, 163.9)	0.383
	Vit. B1 (mg/d)	2.7 (2.7, 2.8)	2.6 (2.6, 2.7)	2.8 (2.7, 2.9)	2.7 (2.6, 2.7)	0.914
	Vit. B6 (mg/d)	2.7 (2.7, 2.8)	2.7 (2.6, 2.7)	2.8 (2.7, 2.8)	2.7 (2.7, 2.7)	0.278
	Vit. B12 (µg/d)	4.8 (4.6, 4.9)	4.9 (4.8, 5.1)	4.8 (4.6, 5.1)	4.9 (4.7, 5.0)	0.196
	Folate (µg/d)	392.4 (385.3, 399.7)	385.9 (380.2, 391.7)	395.8 (385.0, 407.0)	389.6 (385.5, 393.8)	0.719
	Vit. A (µg/d)	915.0 (889.4, 941.4)	916.5 (894.6, 938.9)	922.7 (885.8, 961.0)	917.0 (901.7, 932.5)	0.637
	Vit. D (µg/d)	2.7 (2.6, 2.8)	2.7 (2.6, 2.8)	2.7 (2.6, 2.9)	2.7 (2.7, 2.8)	0.202
	Vit. E (mg/d)	9.3 (9.0, 9.5)	9.1 (8.9, 9.3)	9.4 (9.1, 9.8)	9.2 (9.1, 9.3)	0.345

Table 2, con't

		Taster Status				
		Nontaster	**Taster**	**Supertaster**	**Total**	**P-value**[*]
		Mean Intake gram/d (95%CI)[**]				
Minerals (mg/d)	Ca	1111 (1089, 1134)	1112 (1094, 1130)	1122 (1090, 1154)	1113 (1100, 1126)	0.645
	Zn	11.1 (10.9, 11.3)	11.0 (10.9, 11.2)	11.1 (10.8, 11.4)	11.1 (10.9, 11.2)	0.667
	Fe	17.5 (17.1, 17.9)	17.3 (17.0, 17.6)	17.6 (17.1, 18.2)	17.4 (17.2, 17.6)	0.466

		Diplotype				
		AVI/AVI	**AVI/PAV**	**PAV/PAV**	**Total**	**P-value**[*]
Food		Mean Intake gram/d (95%CI)[**]				
	Broccoli, spring greens, kale	17.1 (14.7, 19.9)	17.3 (15.4, 19.4)	18.0 (14.3, 22.8)	17.4 (15.9, 18.9)	0.607
	Brussel Sprouts	10.0 (8.5, 11.9)	9.2 (8.0, 10.5)	8.2 (6.5, 10.3)	9.2 (8.4, 10.2)	0.307
	Cabbage	13.2 (11.4, 15.4)	11.0 (9.7, 12.5)	10.4 (8.3, 13.0)	11.6 (10.6, 12.7)	0.228
	Cauliflower	12.4 (10.8, 14.3)	12.6 (11.2, 14.2)	13.8 (11.5, 16.6)	12.7 (11.8, 13.8)	0.861
	Turnip	3.1 (2.6, 3.8)	3.2 (2.7, 3.7)	3.5 (2.7, 4.7)	3.2 (2.9, 3.6)	0.716
	Cress vegetables	0.59 (0.48, 0.71)	0.51 (0.43, 0.59)	0.51 (0.39, 0.66)	0.53 (0.48, 0.59)	0.456
	Oranges, grapefruits, etc.	20.6 (16.3, 25.9)	20.4 (17.0, 24.5)	19.6 (14.6, 26.5)	20.3 (17.9, 23.1)	0.389
	Tea	536.0 (438.6, 655.0)	586.1 (498.7, 688.8)	350.7 (231.6, 531.1)	521.5 (459.8, 591.5)	0.424
	Coffee	229.7 (177.3, 297.6)	228.6 (186.5, 280.3)	295.5 (222.5, 392.4)	238.9 (207.5, 275.1)	0.915
	Total Vegetables	226.5 (207.5, 247.1)	234.9 (217.8, 253.2)	238.2 (210.8, 269.2)	232.6 (221.0, 244.9)	0.477
	Total Fruit	246.8 (221.6, 274.8)	233.7 (214.4, 254.8)	245.8 (212.6, 284.1)	239.9 (225.8, 254.9)	0.819
	Total Fruit and Vegetables	501.9 (465.3, 541.5)	495.7 (465.1, 528.4)	508.2 (456.6, 565.7)	499.8 (478.3, 522.4)	0.916
	Red Meat	41.5 (36.4, 47.3)	46.3 (42.1, 51.0)	42.0 (34.8, 50.7)	43.9 (40.9, 47.2)	0.705
	Total Meat	76.9 (67.1, 88.0)	84.2 (76.6, 92.5)	76.9 (64.8, 91.4)	80.4 (74.9, 86.3)	0.978
Nutrient						
Total Energy (kcal)		2222 (2184, 2261)	2210 (2179, 2242)	2263 (2203, 2325)	2223 (2200, 2245)	0.258
Protein (g/d)		85.9 (84.4, 87.4)	85.9 (84.7, 87.2)	86.8 (84.5, 89.1)	86.1 (85.2, 86.9)	0.465
Carbohydrates (g/d)	Total	303.8 (298.3, 309.5)	301.0 (296.5, 305.5)	309.0 (300.2, 318.1)	303.2 (300.0, 306.5)	0.268
	Starch	147.8 (144.7, 151.0)	145.3 (142.8, 147.8)	148.2 (143.4, 153.2)	146.6 (144.8, 148.4)	0.834
	Sugar	141.9 (138.7, 145.1)	142.2 (139.7, 144.8)	146.4 (141.6, 151.5)	142.0 (140.9, 144.7)	0.082
	Fibre	25.0 (24.4, 25.5)	24.4 (23.9, 24.8)	24.9 (24.1, 25.8)	24.7 (24.3, 25.0)	0.883
Fat (g/d)	Total	80.2 (78.5, 82.0)	79.9 (78.4, 81.3)	82.1 (79.5, 84.8)	80.3 (79.3, 81.4)	0.297
	Saturated	26.6 (25.9, 27.3)	26.7 (26.2, 27.3)	27.7 (26.7, 28.7)	26.8 (26.4, 27.2)	0.176
	MUFA	26.1 (25.5, 26.7)	25.9 (25.5, 26.4)	26.7 (25.8, 27.6)	26.1 (25.7, 26.5)	0.342
	PUFA	15.5 (15.2, 15.9)	15.2 (14.9, 15.5)	15.7 (15.2, 16.3)	15.4 (15.2, 15.6)	0.406

25

Table 2, con't

		Diplotype				
		AVI/AVI	**AVI/PAV**	**PAV/PAV**	**Total**	**P-value**
		Mean Intake gram/d (95%CI)[**]				
Vitamins	Vit. C (mg/d)	162.6 (158.5, 166.9)	159.7 (156.4, 163.1)	165.0 (158.5, 171.6)	161.5 (159.1, 163.9)	0.383
	Vit. B1 (mg/d)	2.7 (2.7, 2.8)	2.6 (2.6, 2.7)	2.8 (2.7, 2.9)	2.7 (2.6, 2.7)	0.914
	Vit. B6 (mg/d)	2.7 (2.7, 2.8)	2.7 (2.6, 2.7)	2.8 (2.7, 2.8)	2.7 (2.7, 2.7)	0.278
	Vit. B12 (μg/d)	4.8 (4.6, 4.9)	4.9 (4.8, 5.1)	4.8 (4.6, 5.1)	4.9 (4.7, 5.0)	0.196
	Folate (μg/d)	392.4 (385.3, 399.7)	385.9 (380.2, 391.7)	395.8 (385.0, 407.0)	389.6 (385.5, 393.8)	0.719
	Vit. A (μg/d)	915.0 (889.4, 941.4)	916.5 (894.6, 938.9)	922.7 (885.8, 961.0)	917.0 (901.7, 932.5)	0.637
	Vit. D (μg/d)	2.7 (2.6, 2.8)	2.7 (2.6, 2.8)	2.7 (2.6, 2.9)	2.7 (2.7, 2.8)	0.202
	Vit. E (mg/d)	9.3 (9.0, 9.5)	9.1 (8.9, 9.3)	9.4 (9.1, 9.8)	9.2 (9.1, 9.3)	0.345
Minerals (mg/d)	Ca	1111 (1089, 1134)	1112 (1094, 1130)	1122 (1090, 1154)	1113 (1100, 1126)	0.645
	Zn	11.1 (10.9, 11.3)	11.0 (10.9, 11.2)	11.1 (10.8, 11.4)	11.1 (10.9, 11.2)	0.667
	Fe	17.5 (17.1, 17.9)	17.3 (17.0, 17.6)	17.6 (17.1, 18.2)	17.4 (17.2, 17.6)	0.466

[*]Regression analysis by phenotype or diplotype, [**]Geometric Means

Table 3. Cancer Incidence according to PTC taster status and diplotype

Model	Cases/noncases	Taster Status HR (95%CI)		
		Nontaster	Taster	Supertaster
Model 1 unadjusted	410/2,925	1	1.30 (1.04, 1.62) *p = 0.021*	0.98 (0.72, 1.35) *p = 0.917*
Model 2 age, BMI, smoking status	410/2,912	1	1.28 (1.03, 1.60) *p = 0.027*	1.05 (0.76, 1.44) *p = 0.766*
		Diplotype HR (95%CI)		
		AVI/AVI	AVI/PAV	PAV/PAV
Model 1 unadjusted	58/450	1	0.90 (0.50, 1.62) *p = 0.723*	1.45 (0.71, 2.95) *p = 0.298*
Model 2 age, BMI, smoking status	57/445	1	0.94 (0.52, 1.71) *p = 0.851*	1.19 (0.57, 2.45) *p = 0.643*

Table 4. Cancer Incidence according to PTC taster status and stratified by age

Model	Cases/noncases	Age ≤ 60 y HR (95%CI)		
		Nontaster	Taster	Supertaster
Model 1 unadjusted	170/1,822	1	1.14 (0.82, 1.58) p = 0.426	0.53 (0.30, 0.92) p = 0.025
Model 2 age, BMI, smoking status	170/1,822	1	1.16 (0.84, 1.62) p = 0.361	0.54 (0.31, 0.94) p = 0.031
		Age > 60 y HR (95%CI)		
		Nontaster	Taster	Supertaster
Model 1 unadjusted	240/1,103	1	1.40 (1.04, 1.90) p = 0.029	1.57 (1.06, 2.34) p = 0.026
Model 2 age, BMI, smoking status	240/1,090	1	1.40 (1.03, 1.90) p = 0.030	1.58 (1.06, 2.36) p = 0.024

Supplemental Table 1. Select food intake by PTC taster status and stratified by age

	Nontaster	Taster	Supertaster	Total	P-value*
			Taster Status		
	Nontaster	**Taster**	**Supertaster**	**Total**	**P-value***
			Age ≤ 60 y		
			Mean Intake gram/d (95%CI)**		
Broccoli, spring greens, kale	17.0 (15.8, 18.3)	16.3 (15.4, 17.3)	16.1 (14.7, 17.6)	16.5 (15.8, 17.2)	0.183
Brussel Sprouts	7.0 (6.5, 7.6)	7.0 (6.5, 7.4)	6.9 (6.2, 7.7)	7.0 (6.6, 7.3)	0.108
Cabbage	9.8 (9.1, 10.6)	9.5 (8.9, 10.2)	9.6 (8.6, 10.6)	9.6 (9.2, 10.1)	0.393
Cauliflower	12.5 (11.7, 13.4)	12.3 (11.6, 12.9)	13.0 (11.7, 14.3)	12.5 (12.0, 13.0)	0.382
Turnip	3.2 (2.9, 3.4)	3.3 (3.0, 3.5)	3.7 (3.3, 4.3)	3.3 (3.1, 3.5)	0.118
Cress cruciferous vegetables	0.61 (0.56, 0.68)	0.58 (0.53, 0.63)	0.62 (0.54, 0.71)	0.60 (0.56, 0.63)	0.029
Oranges, grapefruits, etc.	20.5 (18.5, 22.8)	20.9 (19.2, 22.7)	20.9 (17.9, 24.4)	20.8 (19.6, 22.1)	0.976
Tea	401.3 (353.7, 455.2)	551.3 (509.4, 596.7)	485.2 (413.2, 569.8)	485.5 (455.6, 517.3)	0.736
Coffee	228.8 (201.3, 259.9)	238.1 (216.4, 262.0)	221.4 (185.2, 264.9)	232.0 (216.3, 248.9)	0.511
Total Vegetables	244.5 (235.0, 254.3)	240.1 (232.3, 248.1)	249.2 (235.9, 263.2)	243.2 (237.7, 248.8)	0.767
Total Fruit	246.7 (233.3, 260.8)	247.0 (236.1, 258.3)	257.0 (237.9, 277.6)	249.1 (241.4, 257.1)	0.460
Total Fruit and Vegetables	521.9 (502.3, 542.2)	515.5 (499.4, 532.2)	538.2 509.9 (568.0)	522.1 (510.7, 533.8)	0.506
Red Meat	34.6 (31.7, 37.8)	35.9 (33.3, 38.6)	33.7 (29.7, 38.3)	35.2 (33.5, 37.1)	0.341
Total Meat	62.4 (56.8, 68.6)	62.2 (57.6, 67.2)	68.4 (61.0, 76.8)	63.3 (60.0, 66.7)	0.717
			Age > 60 y		
			Mean Intake gram/d (95%CI)**		
Broccoli, spring greens, kale	17.8 (16.3, 19.5)	18.3 (17.1, 19.6)	17.5 (15.1, 20.2)	18.0 (17.1, 18.9)	0.462
Brussel Sprouts	10.2 (9.3, 11.3)	9.9 (9.2, 10.7)	10.8 (9.2, 12.6)	10.1 (9.5, 10.7)	0.490
Cabbage	12.7 (11.6, 14.1)	11.7 (10.9, 12.6)	14.0 (12.2, 16.1)	12.3 (11.7, 13.0)	0.701
Cauliflower	13.5 (12.3, 14.7)	13.6 (12.7, 14.5)	14.0 (12.3, 15.9)	13.5 (12.9, 14.2)	0.915
Turnip	3.7 (3.3, 4.1)	3.5 (3.3, 3.8)	3.6 (3.0, 4.3)	3.6 (3.4, 3.8)	0.095
Cress cruciferous vegetables	0.65 (0.57, 0.73)	0.70 (0.64, 0.77)	0.58 (0.49, 0.69)	0.66 (0.62, 0.71)	0.197
Oranges, grapefruits, etc.	25.7 (22.4, 29.6)	23.6 (21.4, 26.1)	25.1 (20.4, 30.8)	24.4 (22.7, 26.3)	0.878
Tea	482.5 (423.7, 549.4)	500.7, 451.4, 555.3)	482.5 (390.0, 596.9)	492.1 (456.3, 530.7)	0.562
Coffee	256.2 (224.5, 292.4)	253.9 (229.9, 280.3)	229.6 (189.5, 278.0)	251.2 (233.6, 270.1)	0.761
Total Vegetables	262.5 (249.7, 275.9)	250.7 (241.3, 260.5)	263.3 (243.7, 284.5)	255.6 (248.5, 262.8)	0.695
Total Fruit	278.6 (261.4, 296.9)	269.0 (256.3, 282.3)	268.2 (240.6, 299.1)	271.7 (262.1, 281.7)	0.428
Total Fruit and Vegetables	569.0 (543.1, 596.2)	548.4 (530.4, 567.0)	566.0 (525.8, 609.3)	556.6 (542.7, 570.9)	0.612
Red Meat	33.6 (29.9, 37.9)	35.5 (32.8, 38.4)	38.4 (33.6, 43.8)	35.4 (33.3, 37.5)	0.039
Total Meat	58.8 (52.8, 65.5)	65.9 (61.3, 70.9)	78.1 (70.7, 86.3)	65.3 (61.9, 68.9)	0.171

* Regression analysis by phenotype, ** Geometric Means

Supplemental Table 2. Intake of carbohydrates, fat, and salt by PTC taster status and stratified by age.

		Nontaster	Taster	Supertaster	P-value[*]
			Taster Status		
		Age ≤ 60 y			
		Mean Intake gram/d (95%CI)[**]			
Carbohydrates	Total	302.5 (295.7, 309.6)	300.3 (294.5, 306.2)	313.6 (302.5, 325.1)	0.046
	Sugar	138.0 (134.2, 142.0)	138.2 (134.9, 141.5)	145.1 (139.1, 151.3)	0.032
	Fibre	24.7 (24.0, 25.4)	24.4 (23.9, 25.0)	25.2 (24.1, 26.2)	0.257
Fat	Total	80.7 (78.5, 82.9)	80.0 (78.2, 81.9)	82.8 (79.6, 86.1)	0.296
	Saturated	26.7 (25.8, 27.6)	26.6 (25.9, 27.4)	27.5 (26.3, 28.8)	0.549
	MUFA	26.3, (25.5, 27.1)	26.1 (25.4, 26.7)	27. 0 (25.9, 28.1)	0.307
	PUFA	15.8 (15.4, 16.3)	15.6 (15.2, 15.9)	16.4 (15.6, 17.1)	0.090
Total Salt		7.5 (7.4, 7.7)	7.5 (7.3, 7.6)	7.7 (7.4, 7.9)	0.485
		Age > 60 y			
		Mean Intake gram/d (95%CI)[**]			
Carbohydrates	Total	305.7 (296.5, 315.2)	301.2 (294.3, 308.3)	299.2 (284.9, 314.3)	0.468
	Sugar	147.8 (142.6, 153.3)	147.5 (143.6, 151.5)	148.0 (139.7, 156.7)	0.853
	Fibre	25.4 (24.5, 26.4)	24.2 (23.6, 24.9)	24.6 (23.3, 25.9)	0.088
Fat	Total	79.5 (76.7, 82.4)	79.7 (77.4, 82.1)	80.4 (76.1, 85.0)	0.712
	Saturated	26.4 (25.3, 27.5)	27.0 (26.0, 28.0)	27.7 (26.0, 29.5)	0.159
	MUFA	25.8 (24.8, 26.8)	25.8 (24.9, 26.6)	26.0 (24.5, 27.6)	0.811
	PUFA	15.1 (14.5, 15.7)	14.7 (14.3, 15.2)	14.6 (13.7, 15.6)	0.359
Total Salt		7.6 (7.4, 7.8)	7.5 (7.3, 7.7)	7.5 (7.2, 7.9)	0.589

[*] Regression analysis by phenotype, [**]Geometric Means