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ORIGINAL CONTRIBUTION

Bitter taste sensitivity, food intake, and risk of malignant cancer in the UK Women's Cohort Study

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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 ($n=5500$) 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 years, 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 years (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

Abbreviations

BMI	Body mass index
CI	95% confidence interval
FFQ	Food-frequency questionnaire
GI	Gastrointestinal tract
HR	Hazard ratio
OR	Odds ratio
PROP	6-Propylthioluracil
PTC	Phenylthiocarbamide
SES	Socio-economic status
TAS2R38	Taste 2 receptor 38
UKWCS	United Kingdom Women's Cohort Study

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

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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 has 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 1 of the 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, three nonsynonymous single-nucleotide polymorphisms (SNPs) give rise to the amino acid substitutions A49P ($A^{49} \rightarrow P^{49}$), A262V ($A^{262} \rightarrow V^{262}$), and I296V ($I^{296} \rightarrow V^{296}$). These SNPs lead to five haplotypes that are responsible for varying levels of phenotypic PTC/PROP sensitivity in humans. Because of a high level of linkage disequilibrium between A262V and I296V, variation is seen only between A49P and A262V in practice [19]. The PAV haplotype corresponds to a greater sensitivity to certain bitter tastes, whereas the AVI haplotype corresponds to bitter taste insensitivity [19, 20].

A few studies have attempted to explore the relationship between bitter taste sensitivity, diet, and cancer risk. Most of the existing literature has characterized PTC/PROP taster status and food preferences, but did not actually test whether these preferences translate into differences in diet or cancer risk [11, 13, 21]. A limited number of studies have examined the relationship between *TAS2R38* diplotype, differences in diet, and risk of various cancers [22–26]. These studies have yielded conflicting results regarding the impact of diplotype on risk. For example, a case–control study of Korean adults (681 colorectal cancer cases, 1361 controls) reported that the subjects with the AVI/AVI nontaster diplotype were associated with reduced risk of colorectal cancer (OR 0.74, 95% confidence interval [CI]: 0.55, 0.98) compared to subjects with the PAV/PAV taster diplotype [23]. Interestingly, there was no relationship between diplotype and fruit and vegetable, dietary fiber, or energy intake. By contrast, a case–control study of German and Czech populations found that subjects with the AVI/AVI diplotype had increased risk of colorectal cancer (OR 1.33, CI 1.03, 1.72) compared to subjects with PAV/PAV diplotype [25].

In the present study, we examined the association between bitter taste sensitivity (or *TAS2R38* diplotype), food intake, and risk of malignant cancers using data derived from the UK Women's Cohort Study (UKWCS). Our aims were to determine whether any association exists between bitter taste phenotype (or *TAS2R38* diplotype), dietary patterns, and risk of developing malignant cancer.

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 categorized 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 was contacted 1 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 five 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 (http://stephenslab.uchicago.edu/phase/download.html). The present analysis is focused on the three most abundant haplotypes: PAV/PAV, PAV/AVI, and AVI/AVI.

Baseline characteristics and dietary information

Age, height, and weight were self-reported at the time of TaG I study recruitment. If height or weight data were missing from the TaG I data set, then these values were imputed from the baseline data set. Body mass index (BMI) was calculated based on self-reported height (meters) and weight (kg). Ethnicity, smoking status, menopausal status, and adoption of a vegan or vegetarian diet were self-reported at baseline and are categorical or binary variables. Postmenopausal women included women that self-reported undergoing hormone replacement therapy. Dietary data were collected at baseline using a 217-item food-frequency questionnaire (FFQ) that was previously validated using a 4-day food diary [27, 29]. Participant socio-economic status (SES) was categorized as: managerial/professional, intermediate, and routine/manual-based occupation according to the United Kingdom Statistics-Socio-Economic Classification [30]. Intake of specific food items was self-reported in response to the question, "How often have you eaten these foods in the last 12 months?" and included 10 possible responses ranging from "never" to "6+ times per day". Nutrient content of each food item was determined based on *The Composition of Foods* (fifth edition) [31]. Nutrient intakes were calculated by applying a standard portion size to each category and summing the nutrient contribution of each food category to arrive at a total daily nutrient intake. Total fruit and vegetable intake was calculated by summing daily intake of individual fruit (including dried fruits) and vegetable (excluding potatoes) items. Total meat consumption represents the sum of reported frequency of consumption of dishes made from beef, pork, lamb, chicken, and other meats including bacon and offal. Consumption of fruit and vegetables, red meat, and total meat is expressed in grams per day (g/d).

Incident cancer

Incident cancer information for the period from baseline to 4th April 2014 was obtained from the National Health Service Central Register. Time since baseline was used in the survival analysis.

Statistical analysis

Statistical analyses were carried out using Stata, version 15 (Stata Corp., LLC, College Station, TX, USA). The characteristics of the women in the sample were compared across PTC taster phenotype and diplotype using regression analysis for continuous variables and Chi-squared tests for categorical data. The TaG I questionnaire included a section assessing the degree to which an individual liked various foods by asking whether they had "never tried", "like extremely", "like a lot", "like", "like a little", "neither like nor dislike", "dislike a little", "dislike", "dislike a lot", or "dislike extremely" to each of 217 foods. These responses were simplified to: "never tried", "like", "neither like nor dislike", or "dislike". The mean number of "likes", "dislikes", and "never trieds" were compared between PTC taster status groups. All continuous variables are presented as the geometric means with 95% confidence intervals (CI).

Differences in consumption of select fruits and vegetables, total vegetables, total fruits, red meat, and total meat in grams per day across PTC taster status groups and *TAS2R38* diplotypes were assessed using regression analysis. These foods were included based on known bitter taste profiles, content of known bitter phytochemicals, or a relationship to cancer incidence. It was decided not to include coleslaw and low-calorie coleslaw as the fat content might mask the bitterness of the cabbage [32]. Supertasters may also perceive the creaminess as less appealing [33]. Prior to analysis, all foods were transformed using the following formula ($y = \log$ (reported intake [in grams per day] + 0.01 g)), to account for the large number of nonconsumers of any one food item. The procedure above was repeated for phenotypic and genotypic differences between major macronutrients and micronutrients. Risk of developing any malignant cancer according to bitter taste phenotype or *TAS2R38* diplotype was estimated using Cox proportional hazards models to calculate a hazard ratio (HR) and CI. Person-years were calculated from the date that the baseline questionnaire was completed until the first occurrence of either a report of any incident cancer, death or the censor date of the analysis (4th April 2014).

Associations were estimated first using a simple unadjusted model, and then using a model that included age, BMI, and smoking status as potential confounders. The interaction between phenotype and age was also examined given the reported impact of age on bitter taste sensitivity [34, 35]. Interactions between covariates and taster phenotype were examined and the likelihood ratio test was performed to provide statistical evidence for inclusion/exclusion of the interaction terms in the final model.

Ethical approval

One hundred and seventy-four local research ethics committees were contacted and permission to carry out the baseline study was obtained [27]. Further approval for collecting diplotype and phenotype data was granted by the Multiple Research Ethics Committee (Ref 03/10/316).

Results

Baseline characteristics

A total of 3328 women were included in the final analysis. Women were excluded from the final data set if they had extreme BMI (< 16 or > 50 kg/m^2), extreme daily energy intake (< 500 or > 6000 kcal/day), or unreasonable total fruit and vegetable intake (> 3000 g/d). Baseline characteristics of the subjects are shown in toto and separated based on bitter taster phenotype in Table 1. Supertasters were significantly younger, and included a slightly lower percentage of whites and higher percentage of women of Indian/Pakistani origin, although this population represents a small number of individuals in this cohort. Tasters included a higher percentage of premenopausal women. There were no other significant differences in the baseline.

Food and nutrient intake across phenotype and diplotype

Analysis of intake of specific bitter fruit and vegetables, tea, coffee, red meat, and total meat across phenotype (Table 2) showed that there was a small but statistically significant association between phenotype and intake of cress vegetables: mean consumption was 0.62 g/d (CI 0.58, 0.67), 0.63 (CI 0.59, 0.67), and 0.61 (CI 0.54, 0.67) for nontasters, tasters, and supertasters, respectively. There was no evidence of association between taster phenotype and intake of other food items. No significant associations were observed between the major *TAS2R38* diplotypes and intake of particular food items (Table 2). No evidence of significant association was observed between phenotype or diplotype

Table 1 Subject characteristics by PTC taster status

	Nontaster $N=1084$	Taster $N=1714$	Supertaster $N=530$	Total $N=3328$	p value*
Age (years), 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)	1710 (51)	0.011
Socio-economic status *n* (%)					0.356
Professional/managerial	735 (69)	1141 (67)	64 (343)	2217 (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	1064 (99.4)	1658 (99.3)	525 (98.3)	3277 (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 chi-squared test

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

	Taster status [Mean Intake, g/d (95% CI)**]				*p* value*
	Nontaster	Taster	Supertaster	Total	
Food item					
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
Fiber	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/day)	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/day)	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/day)	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/day)	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/day)	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/day)	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/day)	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/day)	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/day)					
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 [Mean intake g/d (95% CI)**]				*p* value*
	AVI/AVI	AVI/PAV	PAV/PAV	Total	
Food item					
Broccoli, spring greens, and 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

Table 2 (continued)

	Diplotype [Mean intake g/d (95% CI)**]				*p* value*
	AVI/AVI	AVI/PAV	PAV/PAV	Total	
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/day)	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/day)					
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
Fiber	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/day)	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/day)	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/day)	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/day)	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/day)	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/day)	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/day)	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/day)	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/day)					
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

and intake of total energy or the macro- and micronutrients examined (Table 2).

Survival analysis

HR and CI for the development of any malignant cancer were estimated across bitter taster phenotype and *TAS2R38* diplotype (Table 3). After adjustment for age, BMI, and smoking status, tasters had a 28% greater risk for malignant cancer incidence (HR 1.28, CI 1.03, 1.60) compared to nontasters (Table 3). No evidence of association was observed between the supertaster phenotype and cancer incidence (HR 1.05, CI 0.76, 1.44). No significant association was observed between *TAS2R38* diplotype and malignant cancer incidence in either model (Table 3). Age was identified as a significant covariate in the overall survival

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	410/2925	1	1.30 (1.04, 1.62) $p=0.021$	0.98 (0.72, 1.35) $p=0.917$
Model 2 age, BMI, and smoking status	410/2912	1	1.28 (1.03, 1.60) $p=0.027$	1.05 (0.76, 1.44) $p=0.766$
Model	Cases/noncases	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, and smoking status	57/445	1	0.94 (0.52, 1.71) $p=0.851$	1.19 (0.57, 2.45) $p=0.643$

analysis ($p<0.001$). We stratified women into two age groups [≤ 60 ($n=1992$) vs. >60 years old ($n=1343$)], and examined the interaction between phenotype and age group. A significant interaction was observed between phenotype and age among supertasters ($p=0.019$) but not for tasters ($p=0.541$). Likelihood ratio test showed that inclusion of the interaction term improves model fit ($p=0.015$). Survival analysis for the main effect of phenotype on malignant cancer risk was performed for each age group. No evidence of association was observed between phenotype and malignant cancer incidence in younger women with the taster phenotype (Table 4). By contrast, younger women with the supertaster phenotype had a lower risk of malignant cancer (fully adjusted HR 0.54, CI 0.31, 0.94) compared to women with the nontaster phenotype (Table 4). Analysis of older women showed that tasters (HR 1.40, CI 1.03, 2.90) and supertasters (HR 1.58, CI 1.06, 2.36) had higher risk of malignant cancer incidence compared to nontasters (Table 4).

Age-stratified dietary characteristics

Given differences observed in the survival analysis after stratifying for age, we stratified the food intake data by age and compared intake across bitter taster phenotype. In the younger women, the only significant association was between cress vegetables and phenotype (Suppl. Table 1). Mean 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) for nontasters, tasters, and supertasters, respectively. In older women, there was a positive association between phenotype and red meat intake ($p=0.039$); supertasters (38.4 g/d, CI 33.6, 43.8) and tasters (35.5 g/d, CI 32.8, 38.4) had a greater mean intake of red meat than nontasters (33.6 g/d, CI 29.9, 37.9). We also

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

Model	Cases/noncases	Age ≤ 60 years HR (95% CI)		
		Nontaster	Taster	Supertaster
Model 1 unadjusted	170/1822	1	1.14 (0.82, 1.58) $p=0.426$	0.53 (0.30, 0.92) $p=0.025$
Model 2 age, BMI, and smoking status	170/1822	1	1.16 (0.84, 1.62) $p=0.361$	0.54 (0.31, 0.94) $p=0.031$
Model	Cases/noncases	Age >60 years HR (95% CI)		
		Nontaster	Taster	Supertaster
Model 1 unadjusted	240/1103	1	1.40 (1.04, 1.90) $p=0.029$	1.57 (1.06, 2.34) $p=0.026$
Model 2 age, BMI, and smoking status	240/1090	1	1.40 (1.03, 1.90) $p=0.030$	1.58 (1.06, 2.36) $p=0.024$

examined the relationship between bitter taster phenotype and intake of food ingredients that may impact bitter perception: carbohydrates, fat, and salt. In younger women, but not older women, there was a significant, positive association between bitter taster phenotype and total carbohydrate and sugar intake (Suppl. Table 2). Among supertasters, mean intake of total carbohydrates and sugar was 313.6 g/d (CI 302.5, 325.1) and 145.1 g/d (CI 139.1, 151.3), respectively. By contrast, mean consumption of total carbohydrates and sugar among nontasters was 302.5 g/d (CI 295.7, 309.6) and 138.0 g/d (CI 134.2, 142.0).

Discussion

In the present study, we examined the relationship between bitter taster phenotype or *TAS2R38* diplotype, food intake, and risk of incident malignant cancer in a population of British women. We hypothesized that women with the taster and supertaster phenotype, or *TAS2R38* PAV/* diplotype, would have reduced bitter fruit and vegetable intake, reduced total fruit and vegetable intake, and an increased risk of incident malignant cancer compared to women with the nontaster phenotype or diplotype. We found that tasters had higher risk of incident malignant cancer compared to nontasters. Age was a significant covariate for malignant cancer risk, and we observed a significant interaction between bitter taste phenotype and age for supertasters, but not nontasters or tasters. For this reason, sub-group analysis was performed (≤ 60 vs. > 60 years old). This analysis showed that, in women over 60 years old, those with either the taster phenotype or the supertaster phenotype were at greater risk of incident malignant cancer than women with the nontaster phenotype. This observed relationship in 60 year old women and younger was different. In this sub-group, there was no association between the taster phenotype and cancer risk, whereas women with the supertaster phenotype had lower risk of incident malignant cancer. The number of supertasters in the cohort was relatively small ($n = 507$ subjects and $n = 51$ cases) and the CI wide.

The reasons for different relationships between phenotype and cancer risk between the age groups and the observed decrease in cancer risk among supertasters are unclear. Examination of the types of cancer prevalent in both the older and younger populations shows that reproductive/hormone-related cancers, GI cancers, and skin cancers were the most common malignancies, and that the differential risk between older and younger women is driven primarily by differences in reproductive/hormone-related cancers (Suppl. Figure 1). This could indicate unidentified interactions between drivers of bitter taste sensitivity and estrogen signalling. Alternatively, the decreased cancer risk could be the result of chance due to the low number of incident cancer cases among younger women with the supertaster phenotype ($n = 51$ cases). Further studies with larger populations of known PTC status, and larger numbers of incident cancer cases, are needed to better test the veracity of the observed relationship with phenotype.

We also examined the relationship between the three most common *TAS2R38* diplotypes, food intake, and risk of incident malignant cancer. We found no evidence of a significant relationship between diplotype and cancer risk. It is unclear how generalizable this lack of association is given the small number of subjects and cancer cases, and the large confidence intervals of the HR estimates. The previous studies have yielded mixed results with regard to the impact of *TAS2R38* diplotype [22–26].

Overall analysis of the relationship between food and nutrient intake and phenotype revealed a few differences. We observed no significant association between taste phenotype and total fruit and vegetable intake, intake of specific bitter fruits and vegetables, or intake of different macro- and micronutrients. The only exception was a small but significant association between intake of cress vegetables and phenotype with supertasters having slightly lower intake of cress vegetables than nontasters. Sub-group analysis showed that tasters and supertasters in the older age sub-group had higher mean red meat intake compared to women with the nontaster phenotype. No other significant differences were observed in this sub-group. Within the younger sub-group, mean cress vegetable intake, mean total carbohydrate intake, and mean sugar intake were positively associated with phenotype. We observed no significant relationship between diplotype and food intake patterns. The lack of clear relationship between bitter taste phenotype and mean intake of these foods observed in this study does not support the popular hypothesis that tasters and supertasters will consume fewer vegetables and, therefore, be at increased risk for developing malignant cancers.

The existing literature for the relationship between PROP/PTC status and fruit and vegetable preference and intake is limited and conflicted [36–39]. One study examined the relationship between PROP taster status and food preferences in a small cohort ($n = 170$) newly diagnosed breast cancer patients who had not yet undergone radiation or chemotherapy, and found that women with the taster and supertaster phenotype gave lower food preferences scores for "cruciferous vegetables", "green vegetables", and "vegetables" [39]. These investigators did not, however, assess intake in this population. Similarly, a cohort study of young children (aged 4–6 years) in the New York City area found that children with the taster phenotype who lived in "healthy food environments" had decreased liking scores for vegetables than children with the nontaster phenotype [37]. By contrast, in a study of 120 Japanese children, there was no association between PROP status and vegetable intake [36].

Yackinous and Guinard investigated the relationship PROP status and dietary intake in a cohort of American college students ($n = 183$), and reported that, with the exception of green salads and fruit, there was no significant effect of phenotype on fruit and vegetable intake in women [40]. No relationship was observed in men.

The lack of evident association between diet and bitter taste sensitivity suggests that other factors are more important in making individual food choices. Cultural and age differences have also been found to influence food choice and preference [13]. Navarro-Allende et al. proposed that genetic haplotypes may be less able to predict diets in more elderly people as neophobia and loss of taste sensitivity with age may both be factors [41]. Furthermore, this sample consists of a low number of smokers and a high number of affluent women. The factors most important in motivating food choice in women with high fruit and vegetable intakes in the UKWCS were found to be health and natural content of the food [42]. The women in this analysis are amongst the highest fruit and vegetable consumers, and may not be representative of the average women in the UK in terms of factors affecting dietary choices.

Studies on the relationship between *TAS2R38* diplotype and diet within the context of cancer have also failed to observe a relationship between diplotype and fruit and vegetable intake [22–26]. Given the large number of TAS2R family members and the differences in their ligand specificity, it is possible that selection of a different TAS2R family member might yield different results. Further study with larger numbers of subjects and a more comprehensive approach to TAS2R diplotype is needed to better understand the impact of bitter taste receptor genotype, food intake, and cancer risk.

Interestingly, we did observe, in the present analysis, that older women with the taster phenotype (5.3% higher) and supertaster phenotype (12.5% higher) had higher mean intake of red meat than women in the nontaster phenotype. It is unclear why tasters and supertasters would consume more red meat than nontasters, but this finding is provocative given the growing body of data which shows that red meat intake is positively correlated with risk of total incident cancers as well as incident breast cancer [5, 43–45]. This difference in red meat intake patterns may play a role in the differences in incident malignant cancer risk in older vs. younger women, but this result requires confirmation by other large cohort studies.

Our study has several limitations which must be considered. First, the number of cancer cases in each phenotype is relatively small especially for the supertaster phenotype. Similarly, the number of subjects genotyped for *TAS2R38* SNPs was relatively small, and the number of cancer cases in this subset of the study population was very low (~ 50 cases). These low numbers of cases limited the power of sub-analyses and precluded an effective analysis of risk for specific cancers. Food intake data in the present study are self-reported. There is, therefore, the potential for over-reporting intake of "healthy" foods and under-reporting intake of "unhealthy" foods as has been noted as a potential confounder for FFQs [46, 47]. Height, body weight, and smoking status were also self-reported and, therefore, susceptible to inaccuracy in reporting. In addition, both body weight and smoking status may have changed between measurement at baseline and cancer diagnosis. Finally, we confined SNP analysis in the present study to differences in *TAS2R38*. Although TAS2R38 is an important member of the TAS2R family and is primarily responsible for differences in PTC/PROP status, it is not the only predictor of liking of bitter foods [16, 48–50]. Moreover, there has been some discussion more recently that supertasters are a group of people who are more sensitive not just to bitter taste, but to spiciness, sweetness, and other food textural cues, owing to a greater number of fungiform papillae on their tongues [51, 52]. This increased number of fungiform papillae is independent of TAS2R38 SNPs, although their expression may be controlled by the same family of receptors [53]. To better identify supertasters in this sample, it would have been ideal to also assess fungiform papillae, but such an assessment would have proven difficult.

Our study has several strengths compared to the previous investigations into the relationship between bitter sensitivity, food intake, and cancer risk. The UKWCS is a large prospective cohort study that has included a long follow-up period. The study includes data on a wide variety of diet and health-related markers, which facilitates careful examination of questions focused on diet and chronic disease. The study is the largest of its kind to investigate the relationship between PTC taster status, food intake, and cancer risk. In addition, we have, for the first time, examined both bitter taster phenotype and *TAS2R38* diplotype and risk of cancer in the same population.

In summary, we report that PTC taster status is positively associated with risk of incident malignant cancer in women over 60 years old. This increased risk was not associated with changes in fruit and vegetable intake, but was associated with mean intake of red meat consumption. Conversely, among women 60 years old and younger, women with the PTC supertaster phenotype had significantly reduced cancer risk. We found no significant association between *TAS2R38* diplotype and food intake patterns, or cancer risk. These results indicate that the relationship between PTC taster status, food intake, and cancer risk is complex, and indicates that future studies on this relationship need to examine relevant endpoints for each aspect of the relationship rather than extrapolate changes in one factor based on the changes in another.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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