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# *TAS2R38* polymorphisms, *Helicobacter pylori* infection and susceptibility to gastric cancer and pre-malignant gastric lesions

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## Abstract

**Background:** Gastric cancer is worldwide the fourth more common cancer type by incidence, and the third by mortality. We analyzed three missense variants of *TAS2R38* gene: rs713598 (A49P), rs1726866 (V262A), and rs10246939 (I296V). These variants and their combination in haplotypes (PAV/tasters or AVI/non-tasters) and diplotypes are responsible for individual

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Author contributions

Daniele Campa conceived the study.

Matteo Giaccherini performed the lab work.

Daniele Campa, Cosmeri Rizzato, Federico Canzian, Ikuko Kato drafted the manuscript.

Manuel Gentiluomo performed data quality control and reconstructed the haplotypes/phenotypes.

Ikuko Kato performed data analysis.

Antonella Lupetti, Lourdes Flores-Luna, Jorge Vivas, Maria Mercedes Bravo, Elena Kasamatsu, Nubia Muñoz, contributed in the data interpretation, analysis and in the drafting of the manuscript.

Conflicts of interest

No author has potential conflicts of interest to disclose.

differences in bitter perception. The single nucleotide polymorphisms and the related phenotypes are known to be associated with susceptibility to Gram-negative bacterial infections, such as *Helicobacter pylori*, and with risk of various cancer types. An association between intermediate tasters (as defined by *TAS2R38* diplotypes) and increased risk of gastric cancer was reported in a Korean population.

**Methods:** we analyzed 2616 individuals of Latin American origin, representing the whole spectrum of lesions from gastritis to gastric cancer.

**Results:** Comparing cancer cases *vs* non-cancers we observed a decrease in risk associated with heterozygous carriers of rs10246939 (p=0.006) and rs1726866 (p=0.003) when compared with homozygotes of the more common allele. Also, the analysis of diplotypes/phenotypes reflected the same association, with super-tasters showing a borderline increased risk of developing gastric cancer compared to medium-tasters (OR=1.63, 95%CI 1.04-2.56, p=0.033). Also, non-tasters showed an increased risk when compared to medium-tasters although not reaching statistical significance (OR=1.58, 95%CI 0.80-2.87, p=0.203). We also tested the interactions between the *TAS2R38* genotypes and *H. pylori cagA* status in a subset of samples and found no interaction.

**Conclusion:** In conclusion, our results suggest only a modest contribution of *TAS2R38* gene genetic variability in gastric cancer etiology.

### Keywords

TAS2R38; genetic polymorphisms; *Helicobacter pylori* ; susceptibility; gastric cancer; pre-malignant gastric lesions

## Introduction

Gastric cancer (GC) is worldwide the fourth more common cancer type by incidence, affecting over one million people annually, and the third by mortality with nearly 800,000 cases dying of the disease (data from 2018, https://gco.iarc.fr/today/, (Ferlay et al. 2019)).

*Helicobacter pylori* (Hp), a Gram-negative bacterium, has been reconized as a class 1 carcinogen for GC by the International Agency for Research on Cancer.(Humans 1994) Hp is the most important established risk factor for GC (Helicobacter and Cancer Collaborative Group 2001) as well as a risk factor for pre-malignant gastric lesions, ranging from chronic gastritis to dysplasia, and gastric ulcer.(Uemura et al. 2001) Even though the involvement of the genetic variability to GC development is relatively understudied, its contribution has been investigatedby genome-wide association studies (GWAS) (Lott and Carvajal-Carmona 2018) and candidate gene studies.(Rizzato et al. 2013a; Durães et al. 2014; Duell et al. 2015)

In humans at least 25 *TAS2R* genes encode for receptors that are responsible for bitter perception. Bitter taste receptor expression has been reported at first in the oral cavity,(Adler et al. 2000) but in the last decades it has been observed in a large number of organs and tissues, including GI tract, testis and upper respiratory airways.(Behrens and Meyerhof 2011) These evidences clearly demonstrate that this group of genes do not have only a role in taste perception and are probably involved in several unrelated functions. Many poison and toxic compounds are bitter and therefore a plausible explanation for their evolution

has been, for many years, their ability to function as gatekeepers to avoid the ingestion of possibly harmful molecules.(Risso et al. 2016b) More recently, instead, mounting evidence suggest that the main function of taste receptors could be the defense of the organism from pathogens, especially Gram-negative bacteria.(Lee et al. 2012) Germline genetic variability in taste receptor genes has been associated with many human traits, such as body mass index (BMI),(Inoue et al. 2013) male infertility,(Gentiluomo et al. 2017) dietary and drinking habits,(Duffy et al. 2004; Diószegi, Llanaj and Ádány 2019) aging,(Campa et al. 2012) smoking behavior,(Risso et al. 2016a) human infections,(Gallo et al. 2016; Cantone et al. 2018) and risk of several cancer types.(Campa et al. 2010; Carrai et al. 2011; Barontini et al. 2017; Gentiluomo et al. 2019) Three single nucleotide polymorphisms (SNPs) in the *TAS2R38* gene, rs713598 (A49P), rs1726866 (V262A), and rs10246939 (I296V), are responsible for amino acid substitutions that modify the ability of the receptor to bind to ligands. In addition through linkage disequilibrium they capture the vast majority of the genetic variability of the gene and have extensively studied in relation to cancer development.(Carrai et al. 2011; Choi and Kim 2019; Lambert et al. 2019)

Considering these premises, the aim of the present study was to analyze the genetic variability of the *TAS2R38* gene in relation to GC and advanced gastric premalignant lesions, in several populations from Latin America where GC risk is high.

## Materials and Methods

### Study population

This study was designed as an ancillary project based on deidentified samples and data previously collected for three studies conducted in a wide range of Latin American populations from low to high risk of GC and representing the whole spectrum of lesions from gastritis to GC. Details concerning eligibility, recruitment, data and sample collection of each study have been published elsewhere.(Muñoz et al. 1996; Kato et al. 2004; Trejo-de la O et al. 2008; Rizzato et al. 2012; Flores-Luna et al. 2013, 2020) Briefly, the original studies include a randomized clinical trial (RCT) for pre-malignant lesions, a GC case-control study and cross-sectional studies for Hp and its associated gastric pathologies. Except for the participants in the RCT and neighborhood controls in the case-controls study, who were in general good health, the other study subjects were recruited from patients seen at gastroenterology or oncology clinics. Subjects were at least 30 years old, and recruited at hospitals from four countries in Latin America, i.e., Venezuela (Tachira province), Colombia (five centers, two from high and three from low risk areas based on gastric cancer incidence), Mexico (Mexico City) and Paraguay (Asunción City) in a varied period from early 1990s to early 2000s. In each site recruitment time spanned no more than three years and all disease groups were collected within the same time period. All study subjects signed an informed consent and ethical clearance was obtained from the committee of each recruitment as well as coordinating centers. While samples were archived regardless of Hp *cagA* status from Venezuelan RCT and case-control study (cases only), Mexican, Colombian, and Paraguayan samples were limited to *cagA*-positive only. *cagA* status was determined by PCR in all studies. For this study, we included 3021 samples.

### Histological diagnosis

For non-cancer cases, five or six gastroscopic biopsies taken from predefined sites were used for histopathological assessment. For each biopsy, the following variables were recorded in a standardized form: type and depth of mucosa biopsied, degrees of neutrophil and monocyte infiltration, active regeneration, glandular atrophy, IM and dysplasia, depth of monocyte infiltration, type of intestinal metaplasia (IM), and quantity of Hp infection (none, difficult to find, easy to find, and abundant). Most of these lesions were graded as none, mild, moderate, or severe and scored as 0–3, respectively. The Hp, monocyte, and neutrophil infiltration scores were calculated as the mean of all evaluable biopsies rated 0–3. Global diagnoses of non-cancer patients were classified into superficial gastritis, chronic gastritis, atrophic gastritis, IM and dysplasia based on the most advanced lesion as previously described.(Muñoz et al. 1996; Kato et al. 2004; Rizzato et al. 2013b; Canzian et al. 2020; Flores-Luna et al. 2020) IMs were further subtyped into types I-III according to Filipe and Jass (Filipe and Jass 1986) and incomplete subtypes, IM II and III, and dysplasia were considered high-grade premalignant lesions based on our previous observation in relation to *cagA*-positive Hp infection.(Plummer et al. 2007) Duodenal ulcer diagnosis without any premalignant lesions were considered ineligible. GC cases were limited to epithelial origin, arising from non-cardiac gastric mucosa, and classified according to the Lauren classification.(Hu et al. 2012)

### SNP selection and genotyping

We analyzed the genetic variability of the *TAS2R38* gene, focusing on three common polymorphisms that determine an amino acid change: rs713598 (A49P), rs1726866 (V262A), and rs10246939 (I296V). The combination of these variants is responsible for phenotypic change in bitter tasting. Genotyping was conducted in 384-well plates using TaqMan technology (ThermoFisher Applied Biosystems, Waltham MA, USA) and KASP technology (LGC Genomics/KBioscience, Hoddesdon, UK), according to the manufacturer's instruction. Duplicated samples (8%) were used as positive control to check the quality of genotyping, and no-template controls were added to each plate. PCR plates were read on a QuantStudio 5 instrument and genotypes called with QuantStudio software (ThermoFisher Applied Biosystem, Waltham MA, USA).

### Haplotype, diplotype and phenotype reconstruction

Haplotypes were reconstructed starting from individuals having 100% call rate (n=2177) using the Phase software.(Stephens and Scheet 2005) Diplotypes were assigned to each individual and a tasting phenotype, coded as a categorical variable, was also assigned to each diplotype combination. Considering the literature,(Choi and Kim 2019) we assigned to the PAV/PAV diplotype the highest degree of bitter sensitivity and to AVI/AVI the lowest one. All other diplotypes were considered as intermediate tasters.

### Data filtering, statistical and bioinformatic analysis

Out of the 3021 samples, for which DNA was extracted, 326 were excluded from the statistical analysis because they had a call rate lower than 66% (less than two genotypes out of the three attempted), leaving 2695 subjects. Additional 79 samples were removed

due to missing covariates as well as ineligible histological types of gastric cancer. The association analyses were limited to the remaining 2616 subjects, that had an average call rate of 94%. The concordance rate between duplicates samples was higher than 98%. For haplotype/phenotype analysis the number was limited to those with a call rate of 100% (n = 2177). We use baseline (pre-treatment) information for the RCT participants.

Response variables in this study were global histological diagnosis, which was divided into 3 groups: low-grade, high-grade pre-malignant lesions and GC, and selected histological parameters, i.e., Hp, monocyte and neutrophil infiltration scores for non-cancer cases only. A conditional logistic regression model to accommodate stratified analyses on country was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for GC vs. non-cancer and those for high-grade vs. low-grade diseases. The ORs for genotypes were calculated using major allele homozygotes as the reference. The ORs were also calculated using both dominant and recessive models. The linear trend with risk was also tested according to the number of minor alleles. Medium-taster phenotype was used as the reference in calculating the ORs for phenotypes. All ORs were adjusted for basic demographic variables (sex, age and educational level), and other risk factors reported previously in this population (cigarette smoking, and duration of refrigerator use),(Kato et al. 2004) most of which, except sex and age, were coded on the ordinal scale. In addition, among non-cancer cases, analysis of covariance was used to estimate covariate-adjusted mean Hp, monocyte, and neutrophil infiltration scores according to receptor phenotypes. These covariates included indicators variables for country (Venezuela as reference), histological group (low- *vs* high-grade) in addition to those described above for logistic regression. All analyses were performed with SAS 9.4. We also tested the interactions between *cagA* status and genotypes/haplotypes/phenotypes in Venezuelan samples only, prior to combining their samples to the others, which were limited to *cagA*-positive specimens. We did not find any significant interactions (supplementary table 1) and thus the main results were based on all countries combined.

## Results

We analyzed the associations between three polymorphic variants of the *TAS2R38* gene, (rs713598 rs1726866, rs10246939) and the risk of developing GC in a population recruited in Latin America. The relevant characteristics of the population are given in table 1, whereas the allelic frequencies are shown in supplementary table 2.

The outcomes of interest were high-grade *vs* low-grade lesions and cancer *vs* non-cancer (high-grade + low-grade pre-malignant lesions). None of the SNPs showed a statistically significant association comparing high-grade *vs* low-grade lesions. Comparing cancer *vs* non-cancer we observed a decrease in risk associated with heterozygous carriers of rs10246939 (p=0.006) and rs1726866 (p=0.003) when compared with homozygotes of the more common allele. Also, heterozygotes for rs713598 showed a lower risk of cancer, although the association did not reach statistical significance (p=0.098). The results are shown in table 2.

We also reconstructed the haplotypes and observed a remarkable difference in haplotype frequencies among the different countries in the study as shown in supplementary table 3.

Additionally, we inferred the tasting phenotypes from the diplotypes. We observed that super-tasters had an increased risk of developing GC compared to medium-tasters (OR=1.63, 95%CI 1.04-2.56, p=0.033). Also, non-tasters showed an increased risk when compared to medium-tasters although not reaching statistical significance (OR=1.58, 95%CI 0.80-2.87, p=0.203). We observed no statistically significant associations comparing high-grade vs low-grade lesions. The results are shown in table 3.

Finally, our results did not show any evidence of interaction between *TAS2R38* polymorphisms and *cagA* status (supplementary table 1). We did not find statistically significant differences in the geno-haplo-phenotype frequencies between *CagA* positive Venezuelan samples and all samples from all other countries (compare supplementary table 1 and supplementary table 4).

## Discussion

*TAS2R38* polymorphisms have been associated with a very long list of human traits such as dietary preferences,(Diószegi, Llanaj and Ádány 2019) smoking behavior,(Baker et al. 2018) alcohol drinking, choice and abuse,(Duffy et al. 2004; Ramos-Lopez et al. 2015) glucose homeostasis,(Dotson et al. 2008) BMI,(Inoue et al. 2013) risk of various cancer types and microbial infection, especially from Gram-negative microorganisms.(Gallo et al. 2016; Cantone et al. 2018)

The haplotypes (PAV and AVI) and diplotypes resulting from the allelic and genotypic combinations explain the individual differences in the perception of bitter molecules. AVI/AVI individuals are considered non-tasters and PAV/PAV have been defined as super-tasters with all the intermediate combinations associated with intermediate tasting phenotypes. The T2R38 receptor has a very strong affinity for a synthetic compound called 6-n-propylthiouracil (PROP), and also binds to several bitter compounds present in vegetables, drugs, smoke particulate and alcoholic (e.g. beer, wine) and non-alcoholic beverages (e.g. coffee and tea).(Mikołajczyk-Stecyna, Malinowska and Chmurzynska 2017) *TAS2R38* polymorphisms, alone or in combination, and PROP sensitivity phenotypes have been studied in relation to colorectal cancer,(Carrai et al. 2011) pancreatic cancer, (Gentiluomo et al. 2019) and GC.(Choi et al. 2016) Considering that the AVI haplotype is supposedly non-functional and therefore gives an obvious disadvantage to AVI/AVI individuals both in respect of defense from infections and in rejecting the ingestion of toxic compounds, a long standing question has been the reason of the relatively high frequency of this population across the world.(Risso et al. 2016b) A possible explanation could be balancing selection, that favors heterozygous individuals who have an intermediate tasting phenotype.(Wooding et al. 2004)

Our results show that heterozygotes for the *TAS2R38*-rs713598 (A49P), *TAS2R38*-rs1726866 (V262A), and/or *TAS2R38*-rs10246939 (I296V) have a lower risk of developing GC. According to tasting phenotype determination (through haplotype and diplotype reconstruction) we observed that medium-tasters had a decreased risk of developing the disease compared to both non-tasters and super-tasters. Cancer is not generally considered to exert selective pressure, due to the fact that arises at older stages in life, however one of the

main etiological factor of GC is the inflammation due to Hp (a Gram-negative bacterium) that colonizes the host at younger age. Thus, it may be possible to explain this association from an evolutionary perspective. The AVI haplotype (conferring the non-taster phenotype) has been associated with increased risk of developing infection even though in very small studies conducted in individuals of Caucasian descent.(Gallo et al. 2016; Cantone et al. 2018) On the other hand, the PAV haplotype and the PAV/PAV combination (super-tasters) have been reported to increase the risk of several cancer types (Mikhina, Motorina and Glekov 1985; Choi et al. 2017) possibly through an interaction with food intake. These observations could lead to hypothesize that a balanced mix of the two haplotypes AVI and PAV could decrease the risk to develop Hp infection and cancer. However, it needs to be noted that several other reports suggest that the AVI haplotype increases the risk of developing neoplastic pathologies (Carrai et al. 2011; Yamaki et al. 2017) or no association at all.(Choi and Kim 2019; Gentiluomo et al. 2019) In addition, the evidences supporting an association between vegetable preferences and intake are heterogenous and conflicting. (Lambert et al. 2019; Smith et al. 2020)

In a recent manuscript Choi and colleagues investigated the role of *TAS2R38*-rs713598, *TAS2R38*-rs1726866, and *TAS2R38*-rs10246939 alone and in combination, in relation to GC in 449 cases and 1,131 controls from Korea. The authors observed that medium-tasters had an increase in risk in developing the disease compared to super-tasters while non-tasters did not show any association.(Choi et al. 2016) These results go in the opposite direction of what we observed in our data. The frequencies of the SNPs are very different in the Korean study and in ours. The two populations are therefore genetically different, which makes a direct comparison of the different findings difficult. It is worth mentioning though that the minor allele frequencies are similar to what expected in both populations when compared to other published work (Risso et al. 2016b) or to the 1000 Genomes project (https://www.internationalgenome.org/1000-genomes-browsers). A limitation of this study is, indeed, that all subjects enrolled in the analysis are from Latin America, which makes hard to generalize our findings.

Hp infection and *cagA* status did not show any interaction with the tasting phenotype and therefore cannot explain the differences observed in the two studies. However we were not well powered to detect interaction between the microorganism and the host genetic variability and it is known that Hp strains are dramatically different in different populations across the globe,(Thorell et al. 2017; Muñoz-Ramirez et al. 2021) it is therefore possible that the difference in the directions of the association depends on different strains of Hp.

Finally, given multiple comparisons made on the two different histological endpoints as well all modest level of the statistical associations found, we cannot rule out the possibility that both associations reflect random statistical fluctuation and chance findings.

In conclusion, our results suggest at best a limited influence of the *TAS2R38* genetic variability in gastric cancer susceptibility.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Data availability

The primary data for this work will be made available to researchers who submit a reasonable request to the PI of the external funding (I. Kato), conditional to approval by all the collaborators. Data will be stripped from all information allowing identification of study participants. The data are not publicly available due to privacy or ethical restrictions.

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**Table 1.**

Distribution of demographic factors of study subjects by histological diagnosis.

| | | Low-grade[a] | (%) | High-grade[b] | (%) | Cancer[c] | (%) | Total | (%) |
|---|---|---|---|---|---|---|---|---|---|
| Sex | Female | 1119 | 53.2% | 179 | 52.0% | 58 | 34.1% | 1356 | 51.8% |
| | Male | 983 | 46.8% | 165 | 48.0% | 112 | 65.9% | 1260 | 48.2% |
| Age | 30-39 | 537 | 25.5% | 38 | 11.0% | 10 | 5.9% | 585 | 22.4% |
| | 40-49 | 751 | 35.7% | 90 | 26.2% | 30 | 17.6% | 871 | 33.3% |
| | 50-59 | 519 | 24.7% | 109 | 31.7% | 35 | 20.6% | 663 | 25.3% |
| | 60+ | 295 | 14.0% | 107 | 31.1% | 95 | 55.9% | 497 | 19.0% |
| Country[d] | Mexico | 101 | 4.8% | 19 | 5.5% | 4 | 2.4% | 124 | 4.7% |
| | Paraguay | 33 | 1.6% | 7 | 2.0% | 9 | 5.3% | 49 | 1.9% |
| | Colombia[e] | 188 | 8.9% | 41 | 11.9% | 23 | 13.5% | 252 | 9.6% |
| | Venezuela | 1780 | 84.7% | 277 | 80.5% | 134 | 78.8% | 2191 | 83.8% |
| | (Hp negative) | 155 | 8.7% | 10 | 3.6% | 2 | 1.5% | 167 | 7.6% |
| | (*cagA* negative) | 555 | 31.2% | 37 | 13.4% | 26 | 19.4% | 618 | 28.2% |
| | (*cagA* positive) | 1070 | 60.1% | 230 | 83.0% | 106 | 79.1% | 1406 | 64.2% |

% represents column percentage.

[a] Low-grade includes superficial gastritis to type I intestinal metaplasia.

[b] High-grade includes types II and III intestinal metaplasia and dysplasia.

[c] Cancer includes non-cardia cancer, divided into 95 intestinal, 62 diffuse and 13 unknown/other cases.

[d] All samples from countries except Venezuela were *cagA* positive.

[e] includes 179 from high-risk area and 73 from low-risk area

**Table 2.**

Associations between *TAS2R38* SNPs and risk of high-grade pre-malignant gastric lesions or gastric cancer.

| SNP | Genotype | Low-grade | High-grade | Cancer | OR[a] (95% CI) | P-value | OR[b] (95% CI) | P-value |
|---|---|---|---|---|---|---|---|---|
| rs10246939 (I296V) | CC | 869 | 141 | 81 | 1.00 | | 1.00 | |
| | CT | 860 | 149 | 51 | 1.04 (0.80-1.34) | 0.783 | **0.58 (0.39-0.85)** | **0.006** |
| | TT | 255 | 45 | 26 | 1.08 (0.74-1.57) | 0.697 | 1.01 (0.61-1.68) | 0.963 |
| | Trend | | | | | 0.678 | | 0.301 |
| | Dominant | 1115 | 194 | 77 | 1.05 (0.82-1.33) | 0.717 | **0.67 (0.47-0.96)** | **0.028** |
| | Recessive | 255 | 45 | 26 | 1.06 (0.74-1.50) | 0.755 | 1.30 (0.81-2.11) | 0.281 |
| rs1726866 (V262A) | GG | 901 | 141 | 77 | 1.00 | | 1.00 | |
| | AG | 835 | 136 | 41 | 1.01 (0.78-1.31) | 0.952 | **0.52 (0.34-0.80)** | **0.003** |
| | AA | 240 | 42 | 19 | 1.07 (0.72-1.57) | 0.866 | 0.87 (0.50-1.54) | 0.641 |
| | Trend | | | | | 0.785 | | 0.099 |
| | Dominant | 1075 | 178 | 60 | 1.02 (0.80-1.31) | 0.872 | **0.60 (0.41-0.88)** | **0.008** |
| | Recessive | 240 | 42 | 19 | 1.06 (0.74-1.53) | 0.748 | 1.04 (0.61-1.78) | 0.605 |
| rs713598 (A49P) | GG | 813 | 128 | 73 | 1.00 | | 1.00 | |
| | GC | 893 | 145 | 62 | 1.00 (0.77-1.31) | 0.997 | 0.72 (0.49-1.06) | 0.098 |
| | CC | 314 | 49 | 23 | 0.96 (0.66-1.38) | 0.811 | 0.72 (0.42-1.23) | 0.231 |
| | Trend | | | | | 0.845 | | 0.119 |
| | Dominant | 1207 | 194 | 85 | 0.99 (0.77-1.27) | 0.931 | 0.72 (0.51-1.03) | 0.074 |
| | Recessive | 314 | 49 | 23 | 0.96 (0.68-1.34) | 0.794 | 0.85 (0.52-1.40) | 0.399 |

[a] odds ratio for high-grade lesions *vs* low-grade, adjusted for age, sex, educational level, length of refrigerator use, smoking status and high starch diet tertile, and stratified by country.

[b] odds ratio for cancer vs non cancer (low+ high-grade), adjusted for age, sex, educational level, length of refrigerator use, smoking status and high starch diet tertile, and stratified by country.

ORs, 95%CIs and p-values in bold are statistically significant (p<0.05).

**Table 3.**

Odds ratios for risk of gastric cancer and high-grade premalignant lesions by taster status.

| Taster status | Low-grade | High-grade | Cancer | OR[a] (95% CI) | P-value | OR[b] (95% CI) | P-value |
|---|---|---|---|---|---|---|---|
| Non-taster | 212 | 37 | 16 | 1.01 (0.68-1.51) | 0.783 | 1.58 (0.80-2.87) | 0.203 |
| Medium-taster | 841 | 141 | 44 | 1.00 | | 1.00 | |
| Super-taster | 723 | 110 | 53 | 0.95 (0.72-1.25) | 0.697 | **1.63 (1.04-2.56)** | **0.033** |

[a] odds ratio for high-grade lesions vs low-grade, adjusted for age, sex, educational level, length of refrigerator use, smoking status and high starch diet tertile, and stratified by country.

[b] odds ratio for cancer vs non-cancer (low+ high-grade), adjusted for age, sex, educational level, length of refrigerator use, smoking status and high starch diet tertile, and stratified by country.

ORs, 95%CIs and p-values in bold are statistically significant ($p<0.05$).