TAS2R38 Bitterness Receptor Genetic Variation and Risk of Gastrointestinal Neoplasm: A Meta-Analysis

Jeong-Hwa Choi\textsuperscript{a,b} and Jeongseon Kim\textsuperscript{a}

\textsuperscript{a}Department of Cancer Biomedical Science Graduate School of Cancer Science and Policy, National Cancer Center, Goyang-si, Gyeonggi-do, Korea; \textsuperscript{b}Department of Food Science and Nutrition, Keimyung University, Dalseo-gu, Daegu, Korea

\section*{ABSTRACT}
Genetic variation in TAS2R38 bitterness taste receptor could alter the efficacy of molecular sensing, hence may be associated with cancer risk. Thus, we performed a meta-analysis to verify the association between the risk of gastrointestinal (GI) neoplasm and TAS2R38 genetic variation. Studies with TAS2R38 diplotype distribution and GI neoplasm phenotypes were searched from PubMed, EMBASE and SCOPUS, and five articles including eight studies were finally selected. The association between diplotype and neoplasm risk was estimated with summarized odds ratios (ORs) and 95\% confidence intervals (CIs), applying of fixed- or random-effects models. The findings suggested TAS2R38 diplotype was not associated with GI neoplasms susceptibility [AVI vs. PAV: OR = 1.03 (95\%CI: 0.97–1.09), AVI/PAV vs. PAV/PAV: OR = 1.05, (95\%CI: 0.94–1.17), AVI/AVI vs. PAV/PAV: OR = 1.04 (95\%CI: 0.94–1.16)]. Because of the presence of heterogeneity under the two genetic models (AVI/AVI vs. PAV/PAV and AVI/AVI vs. PAV/C), further subgroup analyses by ethnicity and neoplasm type were performed. However, results failed to show the neoplasm risk was altered by diplotype. In conclusion, the meta-analysis indicates that TAS2R38 diplotype minimally modified the GI neoplasm risk. Given the limited study size and resources, further well-designed and larger studies are required to validate the true effect of TAS2R38 polymorphisms on neoplasm risk.

\section*{Introduction}
The gastrointestinal (GI) system is not simply an organ for digestion but also a comprehensive sensory tissue (1). Molecular sensing in the GI system differentiates between a variety of externally/externally derived molecules and regulates the subsequent digestive process, including secretion, absorption and transportation. Furthermore, chemosensing in the GI system also recognizes ingested pernicious or non-nutritive compounds, such as drugs and/or food-borne toxins (2) and initiates elimination or neutralization responses, including vomiting or excretion, in the alimentary track to promote survival in response to external/internal stimuli. For these reasons, the GI system, with its molecular sensing, acts as a secondary nutritional gatekeeper along with oral taste perception (3).

Among the major human taste categories, bitterness is considered critical in food preference and rejection, and therefore, bitterness can influence dietary intake and nutritional status (4 – 7). Furthermore, an array of toxins, including phytochemicals and milieu molecules, generally present with bitterness (8). Therefore, lingual and GI perception of bitterness are critical warning systems for survival and disease etiology (9). Type 2 bitter-taste receptors (T2Rs, TAS2Rs), a family of G protein-coupled receptors (GPCRs), mediate the bitterness perception. T2R chemosensing proteins are known to have 25 isoform types and are expressed in multiple tissues, including the oral cavity and GI tract (10). Human TAS2R genes are located on chromosomes 5, 7, and 12 and are highly polymorphic (11). Among the identified genetic variants, the diplotype of TAS2R38, consisting of three single-nucleotide polymorphisms (SNPs) [A49P (145G > C, rs713598), V262A (785T > C, rs1726866) and I296V (886A > G, rs10246939)], has been well described for its functional alterations (12).
Observational and experimental studies have reported that the AVI haplotype showed differential phenotypic and molecular characteristics compared with those of the PAV haplotype (12,13). This evidence suggests that structural changes in T2R38 induced by those genetic variations are decisive factors in bitterness sensitivity and recognition of harmful molecules. Therefore, they might regulate subsequent metabolism and disease susceptibility.

GI cancer is the leading cause of death worldwide (14). The cause of cancer is multifactorial; therefore, multiple studies have been conducted to understand the mechanisms of cancer development and progression, utilizing various approaches that consider dietary, genetic and environmental factors (6,15,16). Recently, an increasing number of studies have been conducted to examine whether TAS2R38 genetic variation is responsible for GI disorders, especially cancer. Researchers have reported that the AVI haplotype or AVI homo-diplotype is associated with the incidence of gastric cancer (GC) and colorectal cancer (CRC) (3,17,18). However, the association between TAS2R38 genetic variation and GI neoplasms is still controversial (3,17). Furthermore, the trend toward the risk-modifying effect of the TAS2R38 diplotype is variable. The potential reason for such inconsistency surrounding TAS2R38 genetic variation and neoplasm incidence is assumed to be lack of power due to small sample sizes, but much remains unconfirmed. Therefore, to obtain a more comprehensive understanding of the role of the T2R38 bitterness receptor in cancer etiology, we performed a meta-analysis to evaluate the association between TAS2R38 diplotype genetic variation and the risk of GI neoplasm.

The relevance of the studies was evaluated by screening the title, abstract and full text. Only human studies were considered for inclusion, and abstracts, conference proceedings and unpublished reports were excluded from the article pool. Manual searching for the references for original and review articles was also performed. Only articles meeting the following inclusion criteria were considered for this meta-analysis: (1) studies assessing the association between neoplasm incidence and the TAS2R38 diplotype/haplotype and (2) studies describing the results as raw data and considering the TAS2R38 diplotype and neoplasm phenotype in any human populations.

In total, 73 items were obtained using the search terms listed above. After removing the duplicates (n = 36), 37 items were evaluated for their relevance to TAS2R38 diplotype related-neoplasm risk. Twenty-nine items were excluded due to inappropriate format or irrelevance (n = 7 and 22). The remaining eight articles were carefully reviewed, and among these, one review and two original articles that did not contain a usable dataset were eliminated. After these steps, five original articles were analyzed for this unadjusted pooled meta-analysis.

**Data Extraction**

The following key information, which is required for meta-analysis, was retrieved from each study: the first author’s name, publication year, study location (country), ethnicity of study subjects, neoplasm type, number of cases and controls, and distribution of TAS2R38 diplotype. Two independent researchers extracted the data and achieved a consensus on all retrieved information.

**Methods**

**Data Sources, Search Strategy, and Selection Criteria**

Figure 1 shows a summary of the literature search procedure applied in our study. Articles in 3 electronic literature databases (PubMed, EMBASE and SCOPUS) published in English and prior to September 2017 were examined. The following keywords were used to obtain potential articles regarding the association between TAS2R38 diplotype and neoplasm risk, independently and then combined: (1) (tas2r38 or t2r38 or tas2r or bitter taste receptor or bitterness receptor or phenylthiocarbamide gene or 6-n-propylthiouracil or prop), (2) (SNP or polymorphism or mutation or genotype or variation or variant), and (3) (cancer or tumor or carcinoma or neoplasm).
groups stratified by ethnicity (Caucasian and non-Caucasian), or neoplasm type [GI cancer only excluding adenomatous polyps (AP), AP only, CRC including AP, or CRC excluding AP)]. Prior to the analyses, we intended to confirm that the genotypic data were in Hardy-Weinberg equilibrium (HWE). However, a few articles did not show the distribution of genotypes in each locus for the TAS2R38 diplotype. Therefore, we could not assess whether the data were in HWE; however, all the original articles reported that the genotype distributions of the controls were in HWE. Other haplotypes of TAS2R38, in addition to PAV and AVI, were evident in each article. However, their association with neoplasm risk was not generally computed due to the rarity. For this reason, only the PAV and AVI diplotype were considered in this study. We estimated unadjusted OR due to the studies without a published OR value. Heterogeneity was evaluated using a Q-statistic and $I^2$ test. For the summary OR estimation, a random effects model was applied when $P < 0.05$ from the heterogeneity of Q-statistics and $I^2 > 50$; otherwise, a fixed model was used. In the case of heterogeneity, subgroup stratified analyses by ethnicity and neoplasm type were also performed to explore the source of the heterogeneity. Sensitivity analysis was also conducted by omitting each study to ascertain the effect of an individual study. Publication bias was examined using a funnel plot, and its skewness was evaluated using Egger’s linear regression test ($P < 0.05$).

The statistical analyses for this study were performed with STATA software (version 14, Stata...
Corporation, College Station, TX). Two-sided \( P \) values <0.05 were considered statistically distinctive.

**Results**

**The Details of the Analyzed Studies**

Using the search terms and procedures described above, 5 articles with 3,060 cases and 4,908 controls were selected for this meta-analysis. Of these articles, Schembre et al. (17) reported the distribution of the \text{TAS2R38\text{\textsuperscript{\textdagger}}\text{\textdagger}}\text{}\text{\textsuperscript{\textdagger}}\text{\textdagger} diplo- and haplotypes in three ethnic groups, and Carrai et al. (3) separately presented this information in two different nationalities. For this reason, these two articles were considered three and two independent studies, respectively, in this meta-analysis. Therefore, the total number of studies included was eight.

Table 1 presents the major characteristics of the studies included in this meta-analysis. The studies were all designed for case-control investigations. Specifically, three and four studies were conducted in Caucasian (3,17) and Asian populations (17–20), respectively. A single study was performed in a Polynesian (native Hawaiian) population (17). Three of the studies focused on the incidence of CRC and the effect of \text{TAS2R38\text{\textsuperscript{\textdagger}}\text{\textdagger}}\text{}\text{\textsuperscript{\textdagger}}\text{\textdagger} genetic variants (3,18). Another three studies investigated AP, a major antecedent of CRC (17). One study by Choi et al. reported the influence of \text{TAS2R38\text{\textsuperscript{\textdagger}}\text{\textdagger}}\text{}\text{\textsuperscript{\textdagger}}\text{\textdagger} genetic variants on GC (19).

Yamaki’s Japanese study reported the association between the \text{TAS2R38\text{\textsuperscript{\textdagger}}\text{\textdagger}}\text{}\text{\textsuperscript{\textdagger}}\text{\textdagger} diplotype and GI cancer (20). However, the study was not stratified by neoplasm type because the number of cases for each cancer type was limited [e.g., GC (\( n = 18 \)) or CRC (\( n = 21 \))]. The prevalence of the PAV haplotype ranged from 0.38 to 0.66 and was more frequently evident in non-Caucasian groups (\( n = 5 \)). Therefore, PAV was considered a reference haplotype in this meta-analysis.

**The Association Between Neoplasm Risk and \text{TAS2R38\text{\textsuperscript{\textdagger}}\text{\textdagger}}\text{}\text{\textsuperscript{\textdagger}}\text{\textdagger} Genetic Variants**

When the effect of the \text{TAS2R38\text{\textsuperscript{\textdagger}}\text{\textdagger}}\text{}\text{\textsuperscript{\textdagger}}\text{\textdagger} haplo-/diplotype was analyzed, none of the genetic analysis models indicated that the \text{TAS2R38\text{\textsuperscript{\textdagger}}\text{\textdagger}}\text{}\text{\textsuperscript{\textdagger}}\text{\textdagger} diplo- or haplotype was associated with a risk for GI neoplasm. The presence of the AVI haplotype and the AVI/PAV diplotype did not modify the risk for GI neoplasms compared with the reference PAV haplotype or PAV/PAV diplotype groups (AVI vs. PAV: \( OR = 1.03, 95\% CI = 0.97–1.09 \), AVI/PAV vs. PAV/PAV: \( OR = 1.05, 95\% CI = 0.94–1.17 \), AVI\textsuperscript{*} vs. PAV/PAV: \( OR = 1.04, 95\% CI = 0.94–1.16 \) (Figs. 2–4). Stratified analyses were conducted to investigate the potential association...
between the TAS2R38 haplo-/diplotype and neoplasia, considering ethnicity and neoplasm type. However, no meaningful genetic effect was observed on neoplasm incidence using any of the genetic models. The results and details of all the analyses are presented in Supporting Information Table S1.
Heterogeneity and Subgroup Analysis

When the risk-modifying effect of the AVI/AVI diplotype was compared with the PAV homo- or heterodiploidy (PAV/PAV or PAV/AVI), heterogeneity was detected (Table 2, $P$ for heterogeneity = 0.006 and $I^2 = 65\%$ for AVI/AVI vs. PAV/PAV, and $p$ for heterogeneity = 0.002 and $I^2 = 69\%$ for AVI/AVI vs. PAV/AVI). To identify the cause of heterogeneity, subgroup analyses based on ethnicity and neoplasm type were performed. We conducted subsequent analyses in Caucasians and non-Caucasians, separately, but the results showed that the TAS2R38 AVI/AVI diplotype was not associated with a risk for GI neoplasms. Additional subgroup analyses were performed in studies of GI cancer only (excluding AP), AP only, CRC (including AP), or CRC (excluding AP). However, the AVI/AVI homo-recessive diplotype was not associated with a risk for GI neoplasms, and after these stratified analyses, heterogeneity was still detected.

Publication Bias Assessment and Sensitivity Test

To estimate the presence of publication bias, funnel plot analysis and Egger’s test were applied. The plots and the $P$ values of the tests provided evidence that no selection or publication bias existed in the meta-analysis (see Supporting Information Table S1 and Figure S1 for the $P$ values and funnel plots). Sensitivity analysis, conducted by omitting individual studies, was performed to evaluate the effect of each study on the pooled OR under all the genetic models. However, the results did not reveal a significant change in the final pooled OR for TAS2R38 genetic variants in the risk for GI neoplasms (data not shown).

Discussion

T2R38 is a type of GCPR chemosensing enzyme universally expressed in multiple tissues, including the GI tract and oral cavity. Therefore, genetic variation in TAS2R38 was thought to be associated with disease risk by modifying dietary intake. The true effect of TAS2R38 genetic variation on the risk for GI neoplasms, independent of dietary intake, has also been a major academic interest, but the findings are inconclusive. Such inconsistency may stem from issues with statistical power and heterogeneity. We therefore examined the risk-modifying effect of the TAS2R38 genetic variant on neoplasm susceptibility using a meta-analysis technique. However, the results from 8 studies with a total of 7968 participants suggest that TAS2R38 genetic variation is not associated with susceptibility to GI neoplasms. Additional subgroup analyses were performed, but they showed that TAS2R38...
Table 2. Stratified analyses of the effect of the\ $\text{TAS2R38}$ diploype (AVI/AVI vs. PAV/PAV or PAV*/\*) on the risk of gastrointestinal neoplasms.

| Neoplasm type                  | Total   | AVI/AVI vs. PAV/PAV | OR (95% CI) | P       | AVI/AVI vs. PAV/* | OR (95% CI) | P       |
|-------------------------------|---------|---------------------|-------------|---------|------------------|-------------|---------|
|                      | N\*     |                     |             | P\*     |                   |             |         |
| Total                 | 8       | 1.067 (0.838–1.360) | 0.006       | 1.055 (0.855–1.301) | 0.002 |
| Ethnicity              |         |                     |             |         |                   |             |         |
| Caucasian              | 3       | 1.116 (0.755–1.648) | 0.034       | 1.178 (0.931–1.491) | 0.099 |
| Non-Caucasian          | 5       | 1.043 (0.747–1.455) | 0.023       | 1.055 (0.855–1.301) | 0.032 |
| Neoplasm type          |         |                     |             |         |                   |             |         |
| Only GIC (excluding AP) | 5       | 1.166 (0.633–1.631) | 0.004       | 1.102 (0.813–1.494) | 0.001 |
| AP                    | 3       | 0.880 (0.681–1.137) | 0.207       | 0.949 (0.770–1.171) | 0.338 |
| CRC (including AP)     | 6       | 1.006 (0.769–1.317) | 0.013       | 1.044 (0.820–1.314) | 0.007 |
| CRC (excluding AP)     | 3       | 1.083 (0.694–1.668) | 0.005       | 1.091 (0.743–1.601) | 0.002 |

OR, odds ratio; 95%CI, 95% confidence interval; GIC, gastrointestinal cancer; AP, adenomatous polyp; CRC, colorectal cancer.

A random effects model was applied when the $P$-value for heterogeneity $<0.05$ and $I^2 > 50$%; otherwise, a fixed effects model was used.

\*Number of studies.

\$P$ value of Q test to assess heterogeneity.

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Epidemiological studies in multiple ethnicities were conducted to examine the association between the T2R38 bitterness receptor and cancer with genetic variation as a modifying factor. Increased risk for colorectal and GI cancer associated with the TAS2R38 AVI/AVI diploype was observed in Germans and Japanese (3,20). A Korean study also showed that PAV/AVI increased the risk for GC (19). The pathogenic role of T2Rs was also observed in an in vitro study with pancreatic cancer cells. T2R38 was involved in pancreatic cancer progression by mediating the activation of key transcription factors (21,22). However, how T2R38 regulates the development and progression of other types of neoplasms, including breast and GI cancer, has not been clearly elucidated (23). To conjecture the potential association between T2R38 and GI cancer, the study of respiratory diseases could be referred. The epithelial expression of T2Rs appeared to be associated with the quorum sensing of bacterial compounds, regulating nitric oxide production and innate immunity (24,). This could also explain why the TAS2R38 diploype showed differential efficacy in bactericidal activity and mucociliary clearance (25,26). In line with this, one putative hypothesis is suggested. The structural changes in T2R38 due to genetic variation might alter the efficacy of the alimentary tract in sensing potential carcinogenic/harmful compounds. This may lead to inappropriate protective responses against those stimuli and may increase the risk for GI cancer (3). Additionally, the regulatory role of bitterness perception and genetic variation in other aspects of physiological metabolism may also be linked to cancer predisposition (1,27,28). For instance, thyrocyte-expressed T2R proteins have been observed (29,30), and bitterness sensitivity and TAS2R38 genetic variation are known to be associated with energy and glucose metabolism. The decisive factors and markers in this mechanism, including glycemic index and load, insulin, insulin resistance, insulin-like growth factor (IGF) and IGF-binding protein, play regulatory roles in cell proliferation and apoptosis and hence may modify cancer risk (31,32). These ideas may support the hypothesis that bitterness intensity and the TAS2R38 variant may be related to the mechanism of carcinogenesis, regardless of dietary modification.

Earlier studies predicted that carriers of the TAS2R38 AVI/AVI diploype or AVI haplotype were at greater risk for cancer compared with those with the PAV/PAV diploype (3,33). However, in Koreans, the AVI/AVI diploype was observed not to increase the risk but rather to protect against CRC (18). Experimental evidence may explain the contrasting findings between these studies. Although individuals with the AVI haploype were less sensitive to chemicals containing a thiourea (N-C=S) moiety, they were still responsive to other bitterness molecules (13). Additionally, independent expression of the AVI transcript was evident (13). This may suggest that the structural changes caused by genetic variation do not simply impair function; these changes may improve sensing for other unknown compounds and hence may initiate appropriate anti-carcinogenic mechanisms. This may also explain why TAS2R38, as well as other T2SR bitterness receptor-encoding genes, show a high degree of polymorphism (11). The perception of bitterness from a variety of natural/artificial substances is mainly mediated by 25 types of T2R bitterness receptors. Deorphanization of T2Rs has led to identification of precise agonists for each isoform. However, single molecules can activate multiple T2Rs, and one T2R can have a wide spectrum of chemical ligands (33,34). Therefore, the genetic diversity in TAS2Rs may provide a benefit in recognition of multiple pernicious chemical
compounds in terms of survival and natural selection in human evolution (11).

Studies have shown the significance of bitterness receptor genetic variation in disease etiology; however, controversies remain. In Czech populations, AVI/AVI was not associated with a risk for CRC. The same null association of AVI/AVI was also observed in native Hawaiian and Japanese- and Caucasian-American populations. The statistical results of the present meta-analysis also suggest that TAS2R38 genetic variation only has a limited association with susceptibility to GI neoplasms across multiple ethnic populations and neoplasm types. A few ideas may be proposed to explain this minimal role of bitterness-related genetic variation in neoplasm risk. First, the distribution of the TAS2R38 haplo-/diplo-type varies among ethnicities. The PAV haplotype was dominant in East Asians but not in populations of Caucasian origin. Furthermore, the AAI haplotype was barely evident in Caucasians and East Asians but is often present in populations of African origin (35). This genetic diversity may affect or hinder the pathogenic role of the TAS2R38 variant, and therefore, it did not appear in the summarized OR in the meta-analysis. Second, as alluded above, the risk-modifying effect of the TAS2R38 variant was different depending on the characteristics of the subjects, ethnicities and neoplasm type. Therefore, differential risk-modifying effects may be nullified in the meta-analysis procedure. To test such ambiguity, as well as to seek the source of heterogeneity, we conducted subgroup analyses. However, the analyses gave us a limited association between the TAS2R38 genetic variant and the risk for GI neoplasms. Further studies should be performed to verify these hypotheses and the true role of T2R38 in GI carcinogenesis.

This meta-analysis provides more comprehensive power to assess the effect of TAS2R38 genetic variation in neoplasm susceptibility; however, potential limitations may exist. First, this meta-analysis was conducted in a population of 3060 patients and 4908 controls. The size of this study is relatively large compared with previous studies, but we cannot dismiss the possibility that a bigger sample size may provide a better understanding of the associations between the genetic polymorphisms and disease. Second, a degree of heterogeneity was observed in the analyses using recessive homozygote and recessive genetic model comparison. Additional stratified analyses by ethnicity and type of neoplasm, as well as sensitivity tests, were conducted, yet those did not answer this issue. The limited number of subjects and different clinical, genetic and environmental characteristics of subjects may act as confounding factors responsible for these results. Last, the number of studies available was limited, especially for stratified analysis, and thus, each subgroup may not appropriately represent the full population characteristics. In addition, most of the studies focused on colorectal neoplasm, but numbers of studies with other GI neoplasm were limited. For these reasons, the current findings should be carefully interpreted.

In summary, using a meta-analysis, we investigated the association between genetic variation in the TAS2R38 bitterness taste receptor and the risk for GI neoplasms. The results indicate that bitterness-related genetic variation does not regulate GI neoplasm susceptibility. Nevertheless, the epidemiological investigation of TAS2R38-related disease etiology, especially for cancer, is still in its infancy. Additional well-designed and larger studies in populations with various genetic and ethnic backgrounds are required.

Author Contributions
JHC designed the study. JHC and JK screened and retrieved the literature and data. JHC analyzed the data and drafted the manuscript. JK provided critical review and undertook responsibility for the overall study content. All authors read and approved the final manuscript.

Disclosure Statement
None of the authors has a conflict of interest.

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ORCID
Jeong-Hwa Choi  
http://orcid.org/0000-0003-4730-6544
Jeongseon Kim  
http://orcid.org/0000-0002-0889-2686

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