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Diet, Glutathione S-Transferases M1 and T1 Gene Polymorphisms and Cancer Risk: A Systematic Review of Observational Studies

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Abstract

Understanding the correlation between genes and diet holds significance in formulating tailored nutritional guidance and enhancing public health initiatives. Consequently, a thorough examination is undertaken to clarify the interplay between varying nutrient intake, Glutathione S-transferases Mu1 and Theta 1 (GSTM1 & T1) gene variants, and susceptibility to cancer development. In this study, we conducted a comprehensive search on MEDLINE/PubMed, Scopus, and Web of Science databases up to April 30, 2023. The review included observational studies that explored the relationship between dietary consumption of acrylamide, fruits, vegetables, plant-based foods, total meat, red meat, coffee, and green tea, as well as the presence of GSTM1 and T1 gene polymorphisms, and the risk of cancer in adult populations. The review findings indicated that high levels of risk factors, particularly red meat, have been linked to a higher chance of developing colorectal cancer risk among individuals with the GSTM1 null genotype. In contrast, heightened levels of protective factors, such as cruciferous vegetables, green tea, coffee, and fruit, have been associated with a decreased risk of lung cancer, adult leukemia, cutaneous melanoma, and lung cancer in individuals exhibiting GST polymorphisms. There is a scarcity of comprehensive studies examining different types of cancer due to various dietary patterns and genetic variations. Research has illuminated the complex interplay among dietary factors, gene polymorphisms, and cancer risk, further comprehensive studies are needed to understand and validate these findings fully. More robust investigations across diverse populations are crucial to developing personalized nutritional interventions and strengthening public health strategies.

Keywords: *Glutathione S-transferases; Cancer; Diet; Observational studies; Review.*

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Introduction

Cancer occurs due to mutations or damage in DNA that disrupt normal cell regulation, leading to uncontrolled cell division and growth (1). The acknowledged risk factors inadequately elucidate the disease's manifestation patterns. Knowledge of the molecular causes of carcinogenesis has advanced significantly, predominantly originating from genetic mutations in most cases. Moreover, an increasing recognition exists regarding the influence of inflammation and the tissue microenvironment, especially on hormone-dependent cancers. However, the predominant genetic mutations implicated in cancer development are primarily non-hereditary. They are associated with the accumulation of somatic mutations and epigenetic changes prompted by incompletely understood environmental factors (2). In 2012, it was predicted that there were 14.1 million diagnosed cases and 8.2 million cancer-related deaths globally (3). For example, in Canada, an estimated 28.2% of deaths in 2021 were linked to cancer (4). Glutathione S-transferases (GSTs), polymorphic biotransformation enzymes, augment detoxification processes and thwart DNA alterations (4-6). GST Mu 1 (GSTM1) and GST theta 1 (GSTT1) are notable members of the GST enzyme family. Polymorphic variants of GSTM1 or GSTT1 include the homozygous null genotypes for the null (deleted) allele (7). Due to a lack of enzyme activity, people with null genotypes may be more susceptible to DNA damage and mutations as well as malignancies of the bladder, lung, colon, head and neck, breast, kidney, and prostate (8-11). There is increasing evidence that polymorphisms of low penetrant genes and environmental exposures such as dietary components and lifestyle may modulate the risk of cancers (12, 13) .Therefore, it was suggested that people with unfavorable genetic polymorphisms would be more susceptible to oxidative damage and could benefit more from the antioxidants included in food. (14). This can facilitate the implementation of personalized dietary interventions in cancer prevention or treatment by identifying specific nutrients with protective effects on the human body. (6). The role of GSTM1/GSTT1 polymorphisms was examined in dietary components and the risk of cancers. In most of these studies, GST genotypes modified relations between dietary factors and cancer susceptibility. (15-18). However, only one review has investigated the association between GSTM1 and GSTT1 gene polymorphisms, dietary factors, and cancer susceptibility, identifying an inverse correlation between the consumption of cruciferous vegetables and the risk of lung cancer among individuals with GSTM1 and GSTT1 null genotypes.(19). Understanding the interaction between genes and dietary patterns is crucial for tailoring individualized nutritional advice and enhancing public health initiatives. (20).

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Consequently, the objectives of this review are as follows: 1) to conduct a thorough exploration of published observational studies that have examined the relationship between nutrient intake, GSTM1 and GSTT1 gene polymorphisms, and cancer risks in adult populations while summarizing the key characteristics and findings of these studies; 2) to identify research gaps and underscore areas that warrant further investigation; 3) to propose recommendations regarding the consumption of various nutrients for cancer prevention.

Methods

We meticulously conducted and drafted this comprehensive systematic literature review in strict accordance with the structured framework specified in the esteemed Cochrane Handbook for Systematic Reviews of Interventions(21). Adhering to the rigorous standards of the internationally recognized Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(22), we outlined the current review process. We took proactive steps by prospectively registering this significant literature review with PROSPERO (CRD42023452067), emphasizing transparency and adherence to best practices in research methodology. Our commitment to following established protocols ensures the credibility and robustness of the findings presented in this systematic review.

Search Strategy

We systematically searched three databases, MEDLINE/PubMed, Scopus, and Web of Science - up to April 30, 2023, to identify relevant content for inclusion in the literature review. No restrictions were considered based on publication dates or languages. The predetermined search terms relating to diet, GSTM1 & GSTT1 gene polymorphisms, and cancer risks are detailed in Table S1. Furthermore, an extensive review of reference lists from pertinent reviews and eligible papers was undertaken to mitigate the risk of overlooking relevant studies. To address the potential impact of publication bias, gray literature was integrated into the search results through searches conducted in institutional repositories, conference proceedings, and preprint databases. Two researchers (SZM and RA) independently evaluated relevant papers' titles and abstracts based on predetermined inclusion criteria. Both reviewers screened all identified articles independently, and their level of agreement was assessed through a pilot screening phase followed by regular meetings to resolve discrepancies and ensure consistency. Full-text articles were reviewed to identify studies that might be pertinent. Similarly, both reviewers independently conducted

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the full-text screening, with disagreements resolved through discussion and, if necessary, by a third reviewer (HM) reaching a consensus.

Eligibility Criteria

Two reviewers, EK and SA, applied specific criteria to evaluate the titles and abstracts of each study and made selections based on the following criteria: 1) studies were required to be conducted on human subjects aged ≥18 years across all ethnicities and genders, 2) studies needed to be designed as observational studies encompassing case-control, nested case-control or case-cohort, cohort, and cross-sectional studies, 3) studies must have investigated cancer incidence with outcomes reported as odds ratios, incidence rate ratios, relative risks, or hazard ratios along with an appropriate assessment of variance, 4) the studies had to focus on various dietary factors as exposures, 5) the analysis should have examined the impact of food items and GSTM1 or GSTT1 genes polymorphisms (gene-diet interaction) on cancer incidence, and 6) comprehensive statistical assessment of the interaction between genes and diet was required. Studies conducted on animal models, individuals below the age of 18, in-vitro studies, review articles, case reports, letters, abstracts, or conference papers, and intervention trials were excluded from the selection process.

Data Extraction

Two reviewers, EK and SA, conducted separate data extraction processes autonomously. Subsequently, a third reviewer (HM) validated the extracted data. The extracted data included the following information: author's surname, study location and publication years, gender distribution, total number of subjects including participants and cases of cancer, average age, duration of the study, dietary intake assessment method and type, cancer site, gene polymorphism type, comparative analysis, controlled variables, and concise overview of effect sizes. To ensure a high level of agreement between the two reviewers, a standardized data extraction form was used, and the reviewers held regular calibration meetings to discuss and resolve any ambiguities. Discrepancies were handled through collaborative discussions between the two reviewers, with unresolved disagreements adjudicated by the third reviewer (HM).

Quality Assessment

Two independent reviewers (SZM and RA) evaluated the methodological quality of the included studies using the Risk of Bias in Non-randomized Studies of Interventions

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(ROBINS-I) framework. (23) . The Cochrane guidelines were employed to assess potential biases in the included papers. (24). A third reviewer (HM) resolved any discrepancies and verified them.

Data Synthesis

The meta-analysis was unfeasible due to the variability of cancer outcomes, limited studies providing data on individual dietary exposures, and the diversity among studies (encompassing different dietary exposures and types of cancer). Consequently, a narrative synthesis was performed to delineate the association between GSTM1 or T1 gene polymorphisms, dietary factors, and cancer susceptibility. The researchers conducted a qualitative analysis within the narrative synthesis to show the relationships between genetic variations and dietary components, focusing on dietary elements such as acrylamide, fruits, vegetables, plant-based foods, total meat consumption, red meat consumption, coffee consumption, and green tea consumption.

Results

Study identification and selection

Our study resulted in 5,306 records, comprising 731 from PubMed, 3,094 from Scopus, and 1,481 from Web of Sciences. After eliminating 1,776 duplicate entries and excluding 1,174 studies involving animals (see Fig. 1), we reviewed the titles and the abstracts of the remaining 2,356 articles. The screening stage resulted in the exclusion of 2,273 papers deemed irrelevant. A thorough assessment of the full texts of the remaining 83 publications resulted in the exclusion of 62 studies for various reasons, as detailed in Table S3. Ultimately, 21 articles involving 25,576 participants, met the eligibility criteria for the systematic review (8, 11-13, 17, 25-39) . Overall, our investigation included 15 case-control studies (8, 11-13, 25, 26, 28-31, 33, 35, 36, 39, 40), four nested case-control studies (32, 34, 37, 38), and two case-cohort studies (17, 27), published between 1998 (29) and 2019 (12). The median sample size across the studies analyzed was 1,105, with a participant range extending from 204 to 25,576. The duration of follow-up exhibited variability across the studies, ranging from a minimum of 1 year. (39)to a maximum of 15 years (8). Although the majority of the studies included both male and female participants, there were three studies. (25, 37, 41) that exclusively focused on women and two studies (28, 38) That solely included male participants. Among the 21 articles reviewed, eight were conducted in the United States. (11, 25, 26, 28, 29, 33, 39, 40), eight in various European countries (12, 13, 17, 27, 34-37), 2 in

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China (8, 38), one in Singapore (32), one in Brazil (30), and one was a multicenter study (31). The studies covered a range of cancers, with four focused on colorectal cancer. (12, 32, 36, 38), three on lung cancer (17, 26, 40), two each on the breast (25, 37), head and neck (28, 30), and prostate cancers (28, 34), as well as colorectal adenoma(29, 35). A single study was identified for each of the following types of cancers: endometrial.(41), kidney (31), colon (33), bladder(39) , cutaneous melanoma (13) , and adult leukemia (8). Vegetable consumption was the most frequently evaluated dietary exposure, with 15 studies addressing this (11, 17, 25, 26, 28, 29, 31-36, 38-40). The remaining exposures were red meat (n = 4)(12, 30, 36, 37), fruit (n = 3)(11, 17, 36), total meat (n = 2) (30, 37), coffee (n = 2) (13, 33), green tea (n = 1)(8), plant-based food (n= 1) (8), and dietary acrylamide (n = 1)(41). In examining habitual dietary intake, nine studies employed validated food frequency questionnaires (FFQ) (8, 17, 25, 27, 28, 30, 36-38). Furthermore, other studies utilized semi-quantitative FFQ (n = 5) (13, 26, 29, 32, 39), validated semi-quantitative FFQ (n = 2) (34, 40), FFQ (n = 3) (12, 31, 35), Validated CARDIA diet history questionnaire (n = 1) (33), and Block FFQ (n = 1)(11) . No eligible studies were identified through the review of reference lists or searches for grey literature.

Risk of bias

As indicated in Table S2, it was observed that 15 of the selected studies exhibited a notable risk of bias, while the remaining studies were determined to have a moderate risk of bias based on the assessment using the Risk of Bias in Non-randomized Studies of Interventions tool (ROBINS). The main factors contributing to the increased bias level were the presence of uncontrolled confounders, participant selection, and exposure assessment.

Vegetable type (raw/cooked), GSTM1/GSTT1 polymorphisms

The study explored the connection between vegetable consumption (both raw and cooked), GSTM1/GSTT1 polymorphisms, and the risk of cancer development. This analysis comprised a total of 11 case-control studies (11, 25, 26, 28, 29, 31, 33, 35, 36, 39, 40), 1 case cohort (17) and three nested case-control studies (32, 34, 38). On the whole, the studies investigated various types of cancers, namely, lung (n = 3) (17, 26, 40), prostate (n = 2) (28, 34), breast (n = 1)(25), head and neck (n = 1) (11), bladder (n = 1) (39), colon (n = 1) (33), and kidney (n = 1) (31), as well as colorectal adenoma (n = 2) (29, 35). The sample size varied from 329 (21) to 3,477 (11) within the studies. Cruciferous vegetables were the most frequently studied category (n = 11) (25, 26, 28, 29, 31, 32, 36, 38, 40), followed by various

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vegetables as a whole (n = 3) (11, 17, 36), glucosinolates (n = 1) (34), and isothiocyanates (n = 1) (39). In their hospital-based case-control study, Ambrosone et al. did not identify any interaction between cruciferous vegetable consumption and the GSTM1 and GSTT1 null/present genotypes concerning breast cancer risk (25). Similarly, there was no observed interaction between head and neck cancer (11), colon cancer (33), and bladder cancer (39) and cruciferous vegetable intake and GSTM1 and GSTT1 null/positive polymorphisms. The case-cohort research conducted by Sørensen et al. found no notable link between the risk of lung cancer and the GSTM1 or GSTT1 genotypes, whether they were null or non-null, in relation to vegetable intake. This discovery indicates that changes in these glutathione S-transferase genes do not notably impact lung cancer risk regarding dietary practices. (17). Carpenter et al. conducted a case-control study within a hospital setting, indicating that high consumption of isothiocyanates among individuals with a GSTM1 homozygous deletion was associated with a significant reduction in the risk of developing lung cancer (OR=0.52; 95% CI = 0.31, 0.86) compared to those possessing at least one copy of GSTM1 (OR = 0.77; 95% CI = 0.49, 1.21) (26). Wang et al., through a case-control study, demonstrated that amplified intake of cruciferous vegetables was linked to a considerable decrease in lung cancer risk among non-smokers with the GSTM1 present genotype (CR = 0.25; 95% CI: 0.07, 0.9) (40). Lastly, Lin et al.'s research conducted in southern California revealed that the consumption of cruciferous vegetables reduced the occurrence of colorectal adenoma in individuals with the GSTM1 null genotype (OR = 0.52; CI = 0.29, 0.93)(29). Moore et al. conducted a study spanning seven centers in Central and Eastern Europe, which revealed that decreased consumption of cruciferous vegetables was associated with elevated kidney cancer risk in individuals with GSTT1 null genotype (odds ratio = 0.54; 95% confidence interval: 0.31, 0.93) (31). Conversely, Joseph et al. found in a population-based case-control study no significant interaction between cruciferous vegetable consumption and GSTM1 and GSTT1-deletion or present genotypes in prostate cancer risk (28). In a study by Steinbrecher et al. within the European Prospective Investigation into Cancer and Nutrition-Heidelberg cohort, individuals with a null GSTM1 genotype exhibited a notably decreased risk of prostate cancer with higher glucosinolates intake (OR = 0.56; 95% CI: 0.35, 0.87) (34). Vogtmann et al. and Seow et al. conducted nested case-control studies that yielded no evidence of an interaction between cruciferous vegetable intake and GSTM1 and GSTT1 null or not null polymorphisms concerning the risk of colorectal cancer (32, 38). Conversely, Turner et al.'s case-control study in the United Kingdom demonstrated a significant reduction in the risk of

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colorectal cancer among individuals with the GSTT1 null genotype who consumed cruciferous vegetables or vegetables in general (OR = 0.4; 95% CI: 0.2, 0.8)(36).

Fruit consumption, GSTM1/GSTT1 polymorphisms

Two case-control and one cohort studies conducted by Gaudet et al. (2004), Turner et al. (2004), and Sørensen et al. (2007) investigated the association between fruit consumption, GST genes polymorphisms, and the risk of developing colorectal cancer. (11) , lung cancer (17), and head and neck cancer (11). The participant numbers varied from 149 (11) to 500 (36). Sørensen et al. observed a significant reduction in lung cancer risk associated with fruit consumption among individuals with one (OR = 0.82; 95% CI: 0.73, 0.93) or two (OR = 0.82; 95% CI: 0.69, 0.97) functional alleles of GSTM1, as well as carriers of two copies of GSTT1 (OR = 0.86; 95% CI: 0.76, 0.97) (17). In contrast, Gaudet et al. (2004) and Turner et al. (2004) reported that neither present nor null genotypes of both GSTM1 and GSTT1 significantly modified fruit intake and head and neck cancer and colorectal cancer risk, respectively.

Red meat consumption, GSTM1/GSTT1 polymorphisms

Several research studies have examined the correlation between the consumption of red meat, genetic variations in GST genes, and the susceptibility to colorectal, breast, and head and neck cancers. Specifically, Klusek et al., Marchioni et al. and Turner et al. (2004) performed case-cohort studies (12, 30, 36) and van der Hel et al. conducted a nested case-control study (37). The participant sample sizes varied, ranging from 103 individuals in the study by Marchioni et al. (2011) to 500 individuals in the study by Turner et al. (2004). The findings by Klusek et al. (2019) indicated a significant increase in the risk of colorectal cancer among individuals with the GSTM1 null genotype who consumed high amounts of red meat (OR = 3.8; 95% CI: 1.6, 9.1), while no such association was observed for individuals with the GSTT1 null genotype in the same study. The other three studies by van der Hel et al. (2004), Marchioni et al. (2011), and Turner et al. (2004) did not identify any significant interactions between red meat intake, GSTM1 null and not null polymorphisms, and the risk of breast, head and neck, and colorectal cancers, respectively.

Total meat consumption, GSTM1/GSTT1 polymorphisms

One nested case-control study (37) and another case-control study (30) Examined the correlation among total meat consumption, GST genotypes, and the susceptibility to breast (n

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= 1) (37) and head and neck (n = 1) cancers. The studies included 229 and 103 cases, respectively. However, neither of these investigations observed a significant interaction between overall meat intake and GSTM1 and GSTT1 null genotype in cancer risk.

Coffee consumption, GSTM1/GSTT1 polymorphisms

Two case-control studies by Fortes et al. (2013) with 304 cases (13) and Slattery et al. (2000) with 1579 cases (33) Examined the association between coffee consumption, GST gene polymorphisms, and the risk of cutaneous melanoma (n = 1) as well as colon cancer (n = 1). Fortes et al. (2013) reported a noteworthy decrease in the risk of cutaneous melanoma among individuals with the null genotype of GSTM1 and GSTT1 (homozygous deletion for GSTM1 and GSTT1) who had a high coffee consumption. Slattery et al. (2000) did not observe a significant interaction between coffee intake and GSTM1 genotypes concerning the risk of colon cancer.

Dietary Acrylamide, GSTM1/GSTT1 polymorphisms

A single case-cohort investigation involving 315 cases examined the relationship between dietary acrylamide, GST gene variations, and susceptibility to endometrial cancer. (41). The findings from this study indicated the absence of a significant relationship between dietary acrylamide and GST null genotype effects on endometrial cancer.

Green tea consumption, GSTM1/GSTT1 polymorphisms

A case-control study by Liu et al.explored the relationship between green tea consumption, GST polymorphisms, and leukemia risk in a cohort of 442 adult cases and controls. The research revealed a notable decrease in leukemia risk among individuals with the GSTT1 null genotype who followed particular green tea consumption patterns. (8).

Plant-based food consumption, GSTM1/GSTT1 polymorphisms

An investigation conducted in a hospital setting reported a case-control study that examined the association between the intake of plant-based foods, genetic variations in GST genes, and the probability of developing head and neck cancer. (30). The findings of this research did not indicate a substantial relationship between the consumption of plant-based foods and specific GSTT1 and GSTM1 null polymorphisms concerning the risk of head and neck cancer.

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Discussion

Diets play a crucial role as environmental determinants in the onset of cancer. While dietary requirements are unique to each individual, there exists a link between genetic diversity and the individual's dietary needs and nutritional status (42). The components of one's diet can impact metabolic pathways, which are modulated by genetic variations, thereby affecting nutritional status and health outcomes. An essential aim of personalized medicine for cancer patients is to establish tailored nutritional recommendations based on individual genetic, metabolomics, and microbiome profiling. GST genetic variants are implicated in aberrant signaling pathways that can contribute to the development of malignancies. However, as critical environmental elements, dietary factors can influence metabolic pathways (43, 44). The primary objective of this investigation was to examine the interactions between nutrients and genes to propose tailored nutritional approaches for the prevention and management of cancer, focusing on GSTM1/GSTT1 polymorphisms. The study examined the interplay between genetic determinants and dietary factors influencing cancer susceptibility. Through a systematic review, we explored the association between GST genetic polymorphisms and diet across various cancer types, marking the first comprehensive analysis of its kind. Our findings indicate a correlation between GST genetic polymorphisms, nutrients, and their distinct impacts on cancer development and vulnerability. Previous research on the GSTM1/GSTT1 polymorphisms in different ethics and cancers with various diets demonstrated controversial results.

In this study, a total of 21 papers employing an observational study design were included. The relationship between GST polymorphisms and nutrition has been investigated in various forms of cancer, given their significant role in cancer prevention and treatment. (45). The interaction between genes and diet highlighted in these studies is essential for enhancing patients' life expectancy. Therefore, it is recommended that further research in personalized medicine and tailored dietary interventions for cancer patients be conducted to leverage these findings for better patient outcomes in terms of survival and life expectancy (46). The superfamily of glutathione S-transferases (GSTs) encompasses five primary classes: Alpha, mu, pi, theta, and zeta. The enzyme GSTT1 is crucial in conjugating reduced glutathione with a wide array of electrophilic and hydrophobic compounds. (47). The genes GSTT1 and GSTT2, classified under the theta class, have been linked to human cancer development . Similarly, the enzymes GSTM1, which are also part of the GST superfamily, exhibit high levels of polymorphism and are located within a gene cluster on chromosome 1p13.3 (48).

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These genetically diverse forms can influence an individual's susceptibility to toxins and carcinogens and the efficacy and toxicity of certain medications. (49). The presence of GSTM1 null mutations has been associated with an increased occurrence of malignancies, possibly due to heightened vulnerability to environmental toxins and carcinogens (50). Perinously a meta-analysis was carried out to examine the correlation between cancer susceptibility and Glutathione S-Transferases (GSTs) in individuals who smoke and consume alcohol. It was determined that the GSTM1-null genotype exhibits a noteworthy association with escalated cancer susceptibility, both independently and when combined with smoking. The GSTT1-null genotype is likewise significantly linked to heightened cancer risks, especially when combined with alcohol consumption (51).Our qualitative analysis provides evidence suggesting that the interplay between GSTM1/GSTT1 polymorphisms, along with the consumption of fruits, red or processed meat, coffee, dietary acrylamide, green tea, and plant-based foods, can have a debatable impact on the predisposition to different types of cancer.

Various studies have investigated the relationship between vegetable consumption and the likelihood of developing different types of cancer. The results have been conflicting. Ambrosone et al., Sørensen et al., Vogtmann et al., and Seow et al. have collectively suggested that there is no significant link between vegetable consumption and the presence of GSTM1/GSTT1 polymorphisms in cancer risk. (17, 25, 38). However, Seow et al. found that a high intake of isothiocyanates from cruciferous vegetables is negatively correlated with colorectal cancer risk. This connection is particularly notable in individuals with GSTM1 and T1 null genotypes due to their slower processing and elimination of these compounds compared to others.(17) . Carpenter et al. (2009) found that individuals with GSTM1 homozygous deletions who consumed isothiocyanates experienced a reduction in lung cancer risk. Additionally, Lin et al. (1998) suggested that cruciferous vegetables may play a role in reducing colorectal adenoma incidence in individuals with the GSTM1 null genotype. This discrepancy in findings is likely attributed to factors such as population diversity and biases related to recall and participant selection (52). Moreover, research by Moore et al. (2007) indicated that individuals carrying the GSTT1 null genotype may benefit from increasing their consumption of cruciferous vegetables to reduce the risk of kidney cancer. Turner et al. (2004) demonstrated that incorporating cruciferous vegetables into the diet could lower the risk of colorectal cancer. Wang et al. (2004) reported that a high intake of cruciferous vegetables was associated with decreased lung cancer risk among non-smokers. Sørensen et

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al. (2007) found that fruits and vegetables can mitigate lung cancer risk, specifically in individuals carrying at least one functional GSTM1 allele. While the relationship between vegetable consumption and cancer risk is complex and still not fully understood, research suggests that consuming cruciferous vegetables may offer some protection against certain types of cancer, particularly in individuals with specific genetic polymorphisms. A study by Sørensen et al. revealed subtle indications of a difference in the probability of lung cancer among those with one functional allele of either GSTT1 or GSTM1 compared to individuals with two alleles. This research suggests a potential correlation between higher consumption of fruits and vegetables and GSTM1 polymorphisms, which refer to variations in the DNA sequence that can affect the function of the GSTM1 gene. According to the study, individuals with a genetic predisposition to lung cancer may reduce their risk by incorporating more fruits and vegetables into their diet, as these foods may help counteract the adverse effects of the GSTM1 polymorphisms. This underscores the importance of maintaining a healthy diet in mitigating the risk of lung cancer, particularly for those who are genetically susceptible to the disease (17). Moreover, Ying Gao et al. worked on the meta-analysis and indicated a positive association between the combined effects of GSTM1/GSTT1 polymorphisms and lung cancer risk (11). In certain epidemiological studies, consuming well-cooked meat has been associated with an increased risk of breast cancer (53). Research has shown that women with the GSTM1 null genotype are at a higher risk of developing breast cancer. The consumption of red meat does not significantly increase the risk of breast cancer in women, regardless of whether they have the GSTM1 genetic makeup or not. Moreover, there is no clear correlation between the amount of red meat consumed and the risk of developing breast cancer. The presence of the GSTM1 genetic makeup does not affect the relationship between red meat consumption and breast cancer risk (37). The meta-analysis in 2016 by Zhiwang Song investigated the relationship between genetic polymorphisms of glutathione S-transferase (GST) M1, GSTT1, and GSTP1 and the risk of breast cancer. It was suggested that GSTT1 null genotype and GSTP1 Ile105Val polymorphism may be potential genetic risk factors for breast cancer (54).a meta-analysis showed a correlation between the glutathione S-transferase M1 (GSTM1) polymorphism suggesting that individuals with the GSTM1 null genotype may be more susceptible to developing CRC (55). According to the studies conducted by van der Hel et al., Marchioni et al., and Turner et al., there is no substantial evidence to suggest a significant correlation between the consumption of red meat and the GST genotypes concerning breast, head, neck, and colorectal cancers. These studies have analyzed various factors such as dietary habits, genetic makeup, and cancer incidence rates, and the findings

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suggest that red meat intake may not be a significant risk factor for the development of these types of cancer. However, it is essential to note that other factors such as lifestyle choices, environmental exposures, and genetic predispositions can also play a role in the development of cancer, and further research is needed to fully understand the relationship between red meat intake and cancer risk (30, 36, 37). Van der Hel et al. observed robust and statistically significant effects of red meat consumption only in postmenopausal women with the GSTM1 genotype present. Klusek et al. also noted that high consumption of red meat significantly interacts with carriers of the GSTM1 null genotype, advising them to avoid high red meat intake to reduce susceptibility to colorectal cancer, which is not significant for the GSTT1 null genotype(12).

Two research studies were undertaken to examine whether there is a link between total meat consumption and GSTM1/GSTT1 polymorphisms in cancer risk. The results of both studies demonstrated no significant correlation between cancer risk, total meat intake, and GST polymorphisms. Van der Hel, et al.'s study, found that individuals with a GSTM1 null genotype faced a higher risk of breast cancer due to insufficient detoxification of carcinogenic substances. While there was no statistical significance, a minor increase in the risk of breast cancer development was observed in those who consumed red meat (37).

An investigation was conducted to find the connection between coffee consumption and the presence of GSTM1/GSTT1 polymorphisms. A significant reduction in the risk of developing cutaneous melanoma was observed in individuals with the GSTM1 and GSTT1 genotypes who drank large amounts of coffee. Cutaneous melanoma is a skin cancer that can be caused by prolonged exposure to UV radiation. Nonetheless, no meaningful connection was discovered between the GSTM1 genotype, coffee intake, and colon cancer. The study by Fortes et al. demonstrated that elevated coffee intake can lower the likelihood of cutaneous melanoma among individuals with the GSTT1 null genotype. The GSTT1 null genotype refers to the absence of the GSTT1 gene in an individual's DNA. This gene encodes for an enzyme that helps the body to detoxify harmful substances, including carcinogens. Thus, people with the GSTT1 null genotype are more vulnerable to the damaging effects of UV radiation, which may result in the development of cutaneous melanoma. This investigation represents the first documented case of elevated coffee consumption reducing the risk of cutaneous melanoma in individuals with the GSTM1 and GSTT1 null genotypes. The study sheds light on the potential protective effects of coffee against skin cancer, especially among

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individuals with specific genetic profiles. More research is needed to confirm and explore the findings (13).

The study conducted by Hogervorst et al. in 2016 investigated the relationship between acrylamide exposure, genetic susceptibility, and the risk of developing endometrial cancer. individuals with the GSTM1 null genotype might convert acrylamide into glycinamide at a higher rate. Glycinamide is considered less toxic than acrylamide but still poses risks. This conversion process indicates that individuals with functional alleles may have a more effective detoxification pathway, potentially reducing their risk of developing endometrial cancer upon exposure to acrylamide. As to the findings, people with the GSTM1 null genotype tend to convert acrylamide into glycinamide at a higher rate. This suggests that exposure to acrylamide increases the risk of endometrial cancer in carrier women with at least one copy of the GSTM1 gene. However, the relationship between GSTM1 and GSTT1 followed a consistent interaction pattern, regardless of the underlying biological mechanisms that governed their interactions with GSTs. These results emphasize the significance of comprehending the genetic components that lead to cancer development and could guide future approaches to prevention and therapy. (41). Furthermore, Xiuxiu Yin et al. 2017 conducted a meta-analysis to investigate the relationship between genetic polymorphisms in glutathione S-transferases M1 (GSTM1) and T1 (GSTT1) genes and the risk of endometrial cancer (EC) and found no significant association between GSTM1 null genotype and an increased risk of endometrial cancer (EC) (56).

The relationship between GST genotypes, plant-based diets, and head and neck cancer was investigated. Nevertheless, according to the study's findings, there was no discernible correlation between these parameters. Nonetheless, Liu and colleagues conducted another study highlighting a connection between green tea consumption, the GSTT1 null genotype, and the risk of developing adult leukemia. However, in the case of the GSTM1 null genotype, no such correlation was seen. The findings are supported by the functional significance of GSTT1 and GSTM1 genes in the human body. These genes play a critical role in metabolizing various environmental carcinogens, which may reduce DNA damage caused by reactive metabolites to hematopoietic stem and progenitor cells. The lack of GSTT1 dramatically raises vulnerability to diepoxybutane-induced sister chromatid exchanges, according to in vitro studies, while the GSTM1 gene does not impact the observed DNA damage effects. These results imply that consuming green tea may be a preventative measure against adult leukemia, particularly for individuals with the GSTT1 null genotype. More

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research is needed to understand further the relationship between these factors and the mechanisms that underlie their effects. (8).

The study conducted by Marchioni and colleagues aimed to investigate the relationship between the intake of plant-based foods, GST gene polymorphisms, and the risk of head and neck cancer development. According to their study's results, no statistically significant association exists between the prevalence of head and neck cancer, the consumption of dietary plant-based foods, and GST genotypes. These findings suggest that dietary habits and GST genotypes do not play a pivotal role in the development of head and neck cancer. The results of this research could potentially inform future studies on the topic and help to develop more effective prevention and treatment strategies. In other words, the study did not find any evidence to suggest that individuals with specific GST gene polymorphisms who consume more plant-based foods are at a higher or lower risk of developing head and neck cancer. Despite the lack of significant findings, the study provides valuable insights into the potential impact of plant-based diets on developing head and neck cancer. It highlights the importance of further research in this area (30).

Strengths and Limitations

This study represents a significant milestone in the field of cancer research, as it undertakes a comprehensive review of the relationship between various dietary patterns and the presence of GSTM1/GSTT1 polymorphisms in cancer risk. Through this study, we aim to gain a deeper understanding of the complex interplay between genetic factors and dietary habits and how they can impact cancer risk. The findings of this study will not only shed light on the underlying mechanisms of cancer development but also provide valuable insights into the prevention and management of this devastating disease. As a result, it provides a comprehensive analysis of the existing primary research literature in this area. Observational studies have indicated that reducing red meat intake and increasing consumption of vegetables, coffee, fruits, and green tea may lower cancer risk, particularly among individuals with the GSTM1/GSTT1 polymorphisms. There is currently a lack of substantial evidence to establish a significant association between the consumption of total meat, plant-based foods, dietary acrylamide, and the risk of developing cancer. While some studies have suggested a potential link, more extensive research is required to confirm reliable conclusions. Therefore, it is always advisable to maintain a balanced and varied diet that includes a healthy mix of both plant-based and animal-based foods. The present study exhibits similar shortcomings to

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prior systematic reviews, such as a constrained selection of eligible papers for specific associations being studied, a notable degree of heterogeneity in diverse study characteristics, and a scarcity of studies carrying out repeated assessments of dietary intake and polymorphism.

Future Research Direction

Further investigation is crucial to determine how the GSTM1 and GSTT1 variants affect cancer risk across various populations and ethnic groups. To obtain a thorough comprehension of GST gene variations that are involved in cancer, it is essential to explore how they interact with environmental factors like dietary habits and exposure to pollutants. Evaluating the long-term implications of GST gene variants on the formation and progression of cancer requires conducting longitudinal studies. Future research will benefit from larger sample sizes and consistent methodology to enhance statistical power and the reliability of findings. To advance personalized medicine for cancer prevention and treatment, functional research must be conducted to elucidate how variations in GST genes and dietary factors influence cancer risks. We can enhance our understanding of cancer development by identifying genetic variations in GST and other related factors associated with cancer onset.

Conclusion

Our systematic review found insufficient evidence to support the modifying influences of GSTM1/GSTT1 polymorphisms on the relationship between dietary factors and cancer susceptibility. Limited research exists regarding the relationship between cancer risk, dietary patterns, and genetic variations. Given that metabolic genotypes can impact risk-modifying factors, controlled trials involving various populations are warranted to confirm the gene-diet interaction and enhance comprehension of the disease's etiology. Studies suggest that high consumption of red meat may increase the risk of colorectal cancer in people with the GSTM1 null genotype. Consuming fruits, green tea, coffee, and cruciferous vegetables may reduce the incidence of adult leukemia, cutaneous melanoma, and lung cancer in people with GSTM1/GSTT1 polymorphisms. Nevertheless, the existing studies on the interplay between dietary factors, GSTM1 and T1 gene polymorphisms, and cancer risk are currently limited. Comprehensive studies exploring the correlation of various dietary patterns and genetic variations with different types of cancer are scarce. The presence of polymorphisms in genes responsible for nutrient metabolism can significantly impact how nutrition affects cancer development. Modifying dietary recommendations for cancer prevention and control based

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on individual genotypes is imperative. Advancements in nutritional genomics can pave the way for personalized preventive and therapeutic strategies for cancer patients.

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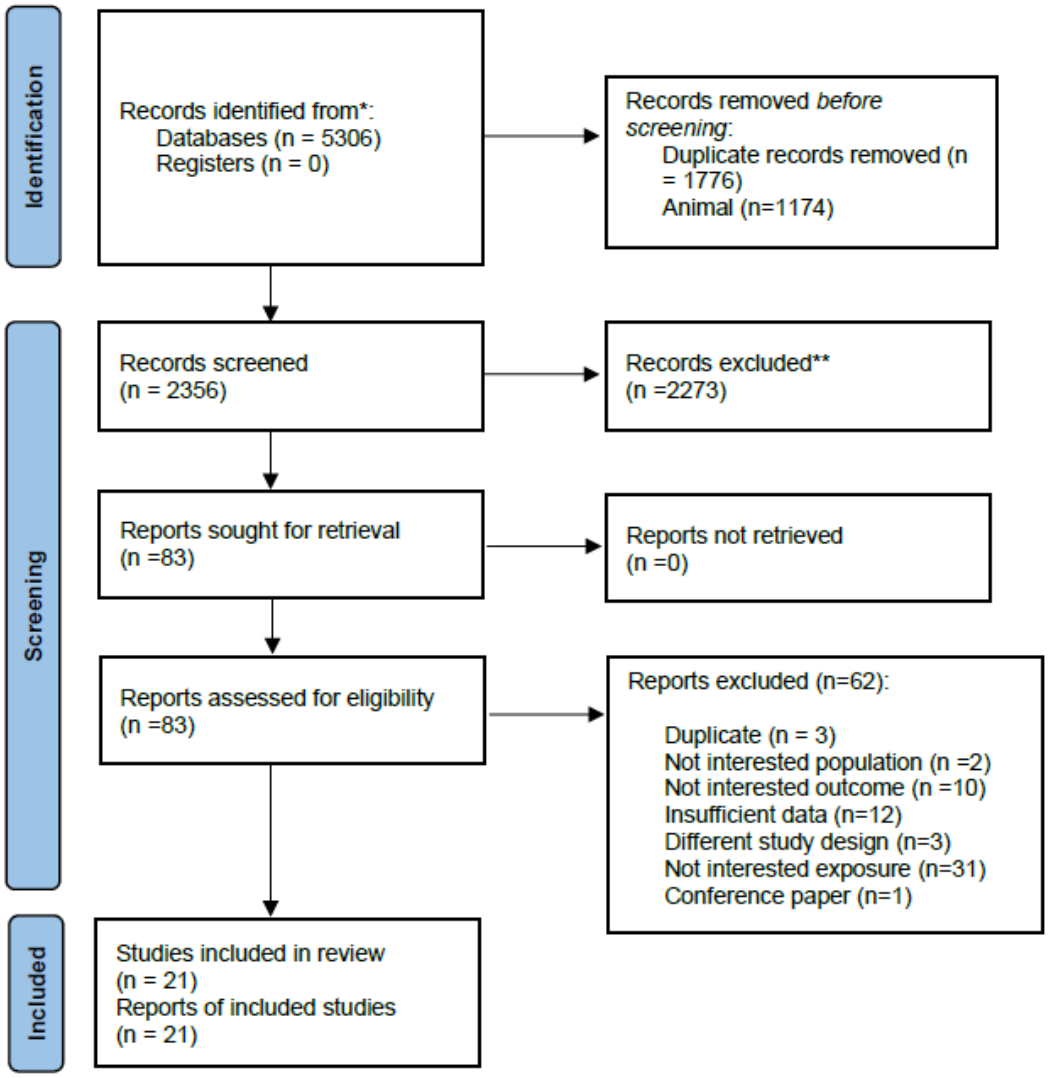

Figure 1. Literature search and review flow diagram for selection of studies.

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Table 1. Overview of the reviewed source

Author, Years, Country (ref.)	Study name/design	Participant/cases/control	Age/Follow-up	Cancer site	Dietary component	Dietary assessment	Polymorphism gene	Comparison	OR/RR/HR/IRR (95%CI)	Variable controlled
Ambrosone, 2004, USA (57)	-/Hospital based-case-control study	1,550 women/740/810	<50 & ≥50 years/5 years	Breast cancer	Broccoli	170-item, validated FFQ	GSTM1 & GSTT1 (null/not null)	≤380 vs. >966 g/mo	GSTM1 (premenopausal women): Null, 1.0 (0.4, 3.1) Not null, 0.7 (0.1, 1.2) GSTT1 (premenopausal women): Null, 0.3 (0.1, 1.6) Not null, 0.7 (0.3, 1.8)	1,5,15,22,23
								≤234 vs. >635 g/mo	GSTM1 (postmenopausal women): Null, 0.5 (0.2, 1.5) Not null, 1.0 (0.4, 3.0) GSTT1 (postmenopausal women): Null, 2.1 (0.5, 9.7)	

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									Not null, 0.7 (0.3, 1.8)	
Carpenter, 2009, USA (26)	-/Hospital based-case-control study	933 both sexes/311/622	63.05 years/ 3 years	Lung cancer	Isothiocyanate content (3 vegetables, broccoli, cauliflower, cabbage)	Semi-quantitative-FFQ	GSTM1 (null/not null)	<40 vs. ≥40 μMol	Null, 0.52 (0.31, 0.86) Not null, 0.77 (0.49, 1.21)	1,24,25
Fortes, 2013, Italy (13)	-/Hospital based-case-control study	609 both sexes/304/305	52.05 years/2 years	Cutaneous melanoma	Coffee	36-item, semi-quantitative-FFQ	GSTM1 & GSTT1 (null/active)	Daily or less than daily vs. More than daily	GSTM1: Null, 0.42 (0.2, 0.89) Active, 0.56 (0.26, 1.22) GSTT1: Null, 0.01 (0.001, 0.17) Active, 0.79 (0.44, 1.39)	1,24,15, 25,26,27 ,28
Gaudet, 2004, USA (11)	-/Hospital based-case-control study	329 both sexes/149/180	20->70 years/3 years	Head & neck cancer	All fruits	Modified 44-item, Block FFQ	GSTM1 & GSTT1 (null/not null)	<14 vs. ≥14 servings/week	GSTM1: Null, 0.68 (0.29, 1.6) Not null, 0.78 (0.36, 1.7) GSTT1: Null, 1.1 (0.36, 3.5) Not null, 0.73 (0.39, 1.4)	1,24,29, 7,18
					All vegetables	Modified 44-	GSTM1 & GSTT1 (not	<29.5 vs. ≥29.5	GSTM1: Null, 1.5 (0.66, 3.3)	

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						item, Block FFQ	null)	servings/week	Not null, 1.5 (0.67, 3.2) GSTT1: Null, 1.9 (0.67, 5.6) Not null, 1.7 (0.89, 3.1)	
Hogervorst, 2016, Netherland (58)	Netherlands Cohort Study/Case-cohort study	2,589 women/315/1474	61.4 years/11.3 years	Endometrial cancer	Dietary acrylamide	150-item, validated FFQ	GSTM1 & GSTT1 (1 or 2 copies/deleted), all SNP	T1 vs. T3	GSTM1 (all women): 1or 2 copies, 1.66 (1.00, 2.74) Deleted, 0.93 (0.39, 2.21) GSTT1 (all women): 1or 2 copies, 1.60 (1.04, 2.44) Deleted, 0.28 (0.03, 2.77)	1,2,3,4,5,6,7,8,9,10,22
Joseph, 2004, USA (28)	WNYDS/ Population based-case-control study	428 men/965/537	70 years/4 years	Prostate cancer	Cruciferous vegetables	172-item, validated FFQ	GSTM1 & GSTT1 (null/not null)	<1,157 vs. ≥1158 g/mo	GSTM1: Null, 0.98 (0.53, 1.82) Not null, 0.62 (0.33, 1.17) GSTT1: Null, 0.92 (0.40, 2.12) Not null, 0.87 (0.52, 1.12)	1,30,31
Klusek,	-/Hospital	301 non-	38-81	Colorect	Red meat	FFQ	GSTM1 &	<6 vs. ≥7	GSTM1:	1,24

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2019, Poland (12)	based-case-control study	smokers of both sexes/197/104	years/3 years	al cancer			GSTT1 (null)	times/week vs.	Null, 3.8 (1.6, 9.1) GSTT1: Null, 1.9 (0.4, 8.5)	
Liu, 2015, China (8)	-/Hospital based-case-control study	884 both sexes/442/442	44.4 years/15 years	Adult leukemia	Green tea	Validated FFQ	GSTT1 (normal/null)	≤10 vs. >20 years	GSTT1: Null, 0.19 (0.07, 0.55) Normal, 0.42 (0.22, 0.81)	1,7,15,18,20,24,20,32
								<1 vs. ≥2 cup/d	GSTT1: Null, 0.13 (0.05, 0.32) Normal, 0.29 (0.16, 0.55)	
								≤500 vs. .100 g/years	GSTT1: Null, 0.34 (0.18, 0.65) Normal, 0.2 (0.08, 0.55)	
L. van der Hel, 2004, Netherland (37)	The Netherlands /Nested case–control study	551 women/229/264	47.2 years/10 years	Breast cancer	Total meat	Validated FFQ	GSTM1 (null/not null)	<75 vs. ≥100 g/d	GSTM1: Null, 1.75 (0.90, 3.40) Not null, 1.06 (0.54, 2.10)	1,5,6,10,18,20,21,22
					Red meat	Validated FFQ	GSTM1 (null/not null)	<30 vs. ≥45 g/d	GSTM1: Null, 2.11 (1.08, 4.14) Not null, 1.80 (0.92,	

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									3.51)	
Lin, 1998, USA (29)	-/Hospital based-case-control study	966 both sexes/459/507	62 years/2 years	Colorectal adenomas	Cruciferous vegetables	126-item, semi-quantitative-FFQ	GSTM1 (null/not null)	Q1 (0.6 serving/week) vs. Q4 (7.3 (null) or 8.1 (not null) serving/week)	GSTM1: Null, 0.52 (0.29, 0.93) Not null, 0.95(0.72, 1.1)	1,6,10,11,24
Marchioni, 2011, Brazil (30)	-/Hospital based-case-control study	204 both sexes/103/101	53 years/3 years	Head & neck cancer	Plant-based foods	Validated FFQ	GSTM1 (null/not null)	≤23 vs ≥32.5 portions/week	GSTM1: Null, 0.91 (0.19, 4.28) Not null, 0.65(0.23, 1.85)	1,6,18,24
					All meats	Validated FFQ	GSTM1 (null/not null)	≤2.5 vs ≥4 portions/week	GSTM1: Null, 10.79 (2.17, 53.64) Not null, 0.45 (0.14, 1.45)	
					Beef	Validated FFQ	GSTM1 (null/not null)	≤6 vs ≥8 portions/week	GSTM1: Null, 3.69 (0.77, 17.66) Not null, 0.91 (0.3, 2.73)	
Moore, 2007, Seven centers	The Central and Eastern European Renal Cell	2652 both sexes/1097/1247	20-79 years/4 years	Kidney cancer	Cruciferous vegetables	23-item, FFQ	GSTM1 & GSTT1 (null/active)	Never to <1/month vs. ≥1/week to daily	GSTM1: Null, 0.76 (0.54, 1.06) Active, 0.82 (0.52,	1,24

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(31)	Cancer Study/ Hospital based-case-control study								1.16) GSTT1: Null, 0.54 (0.31, 0.93) Active, 0.85 (0.66, 1.11)	
Steinbrecher, 2010, Germany (34)	EPIC-Heidelberg study/ Nested case-control study	740 both sexes/248/492	58.1 years/4 years	Prostate Cancer	Glucosinolate Intake	145-item, validated semi-quantitative-FFQ	GSTM1 & GSTT1 (+/+, +/0, 0/0)	per 10 mg/d increment	GSTM1: +/+, 1.24 (0.51, 3.03) +/0, 0.82 (0.55, 1.22) 0/0, 0.67 (0.45, 0.98) GSTT1: +/+, 0.89 (0.57, 1.38) +/0, 0.70 (0.48, 1.02) 0/0, 0.78 (0.38, 1.58)	30,31
Sørensen, 2007, Denmark (17)	DCH/Case-cohort study	1,197 both sexes/430/767	50-70 years/4 years	Lung cancer	Fruit	192-item, validated FFQ	GSTM1 & GSTT1 (at least 1 allele (+/+ or +/0)/no allele (0/0))	Per 50% increase	GSTM1: +/+, 0.82 (0.69, 0.97) +/0, 0.82 (0.73, 0.93) 0/0, 0.99 (0.90, 1.09) GSTT1: +/+, 0.86 (0.76, 0.97) +/0, 0.94 (0.84,	6,7,8,11

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									1.05) 0/0, 1.01 (0.87, 1.18)	
					All types of vegetable (cooked/raw)	192-item, validated FFQ	GSTM1 & GSTT1 (at least 1 allele (+/+ or +/0)/no allele (0/0))	Per 50% increase	GSTM1: +/+, 0.79 (0.55, 1.14) +/0, 0.91 (0.78, 1.06) 0/0, 1.14 (1.00, 1.30) GSTT1: +/+, 1.00 (0.86, 1.16) +/0, 1.04 (0.90, 1.21) 0/0, 1.09 (0.89, 1.33)	
Seow, 2002, Singapore (32)	Singapore Chinese Health Study/ Nested case-control study	1,407 both sexes/213/1194	45-74 years/5 years	Colorectal cancer	Cruciferous vegetables	165-item, semi-quantitative-FFQ	GSTM1 & GSTT1 (null, not null)	≤5.16 μmol/1000 kcal vs. > 5.16 μmol/1000 kcal	GSTM1: Null, 0.85 (0.54, 1.35) Not null, 0.71 (0.45, 1.14) GSTT1: Null, 0.63 (0.37, 1.07) Not null, 0.97 (0.64, 1.47)	5,6,12,15,18,24,33 (32)

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Slattery, 2000, USA (33)	-/ population-based case-control study	3,477 both sexes/157 1898 9/	65 years/3 years	Colon cancer	Cruciferous vegetable	Validated CARDIA diet history questionnaire	GSTM1 (null, present)	None serving/week vs. >3 serving/week	GSTM1: Null, 1.03 (0.75, 1.43) Present, 0.96 (0.69, 1.33)	1,5,7,10, 12,24
					Coffee	Validated CARDIA diet history questionnaire	GSTM1 (null, present)	None vs. ≥6 servig/day	GSTM1: Null, 1.03 (0.74, 1.43) Present, 0.94 (0.66, 1.31)	
Tijhuis, 2005, Netherlands (35)	-/Endoscopy-based case-control study	1,444 both sexes/746/ 698	55.2 years/5 years	Colorectal adenomas	Cruciferous vegetable	FFQ	GSTM1 & GSTT1 (null, present)	≤129 vs. >129 g/week	GSTM1: Null, 1.12 (0.83, 1.53) Present, 1.30 (0.94, 1.79) GSTT1: Null, 1.08 (0.64, 1.80) Present, 1.15 (0.76, 1.73)	1,10,24, 34
Turner, 2004, UK (36)	-/ Case-control study	1,242 both sexes/500/ 742	45-80 years/4 years	Colorectal cancer	Fruit	Validated FFQ	GSTT1 (null)	≤31 vs >31 servings/month	GSTT1: Null, 0.6 (0.3, 1.1)	-
					Vegetables	Validate	GSTT1 (null)	≤31 vs >31	GSTT1:	

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						d FFQ		servings/month	Null, 0.3 (0.1, 0.6)	
					Cruciferous vegetable	Validated FFQ	GSTT1 (null)	≤31 vs >31 servings/month	GSTT1: Null, 0.4 (0.2, 0.8)	
					Red meat	Validated FFQ	GSTT1 (null)	≤14 vs >14 servings/month	GSTT1: Null, 1.3 (0.7, 2.5)	
Vogtmann, 2014, China (38)	SMHS/Nested case–control study	1,013 men/340/673	40-74 years/6 years	Colorectal cancer	Cruciferous vegetable	Validated FFQ	GSTM1 & GSTT1 (null, not null)	T1 vs. T3	GSTM1: Null, 1.04 (0.66, 1.63) Not null, 1.28 (0.73, 2.23) GSTT1: Null, 1.11 (0.68, 1.81) Not null, 1.11 (0.67, 1.82)	1,5,6,10,12,13,14,15,16,17,18,19,22
Wang, 2004, USA (40)	-/ Case-control study	1,655 both sexes/716/934	61.5/8 years	Lung cancer	Cruciferous vegetable	126-item, semi-quantitative-validated-FFQ	GSTM1 & GSTT1 (null, present)	<1.12 vs. 3.01 servings/week	Non-smoker GSTM1: Null, 0.6 (0.23, 1.58) Present, 0.67 (0.25, 1.8) GSTT1: Null, 0.28 (0.06, 1.27) Present, 0.25 (0.07, 0.9)	1,10,24

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									Ex-smoker GSTM1: Null, 1.23 (0.79, 1.92) Present, 0.99 (0.63, 1.57) GSTT1: Null, 0.94 (0.47, 1.88) Present, 1.18 (0.67, 2.08)	1,24
									Current smoker GSTM1: Null, 1.07 (0.6, 1.91) Present, 0.54 (0.29, 1.01) GSTT1: Null, 0.67 (0.26, 1.77) Present, 0.64 (0.3, 1.39)	1,24
Zhao, 2007, USA (39)	-/ Case-control study	1,405 both sexes/697/708	62.9 years/1 year	Bladder cancer	Isothiocyanates	135-item, semi-quantitative-FFQ	GSTM1 & GSTT1 (null, positive)	<0.33 vs. ≥0.33 mg/100 kcal	Never smokers GSTM1: Null, 1.3 (0.75, 2.26) Positive, 0.8 (0.45, 1.4) GSTT1: Null, 1.6 (0.6, 4.26)	1,24,29

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									Positive, 0.93 (0.61, 1.43) Current smokers GSTM1: Null, 0.49 (0.33, 0.74) Positive, 0.59 (0.39, 0.88) GSTT1: Null, 0.38 (0.19, 0.74) Positive, 0.58 (0.42, 0.79)	

Abbreviations: CI, confidence intervals; DCH, Diet, Cancer and Health; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; IRR, incidence rate ratio; *GSTT1:* Glutathione S-transferase T1; *GSTM1:* Glutathione S-transferase M1; HR, hazard ratio; mo, month; OR, odds ratio; Q, quartiles; RR, risk ratio; ref, references; SMHS, Shanghai Men's Health Study; SNPs, single nucleotide polymorphisms; T, tertiles; WNYDS, (28)Western New York Diet Study.

[a] age (1), parity (n children) (2), ever use of oral contraceptives (3), ever use of postmenopausal hormone use (4), body mass index (5), current smoking (6), quantity of smoking (7), smoking intensity (8), family history of endometrial cancer (9), energy intake (10), intakes of fruits & vegetables (11), physical activity (12), red meat intake (13), total meat (14), education (15), income (16), occupation (17), alcohol consumption (18), family history of cancer (19), town (20), menopausal status (21), age at menarche (22), family history of breast cancer (23), gender (24), hair color (25), skin phototype (26), common nevi (27), sunburns episodes in childhood (28),race (29), family history of prostate cancer (30), total vegetable consumption (31), study site (32), saturated fat (33), folate intake (34).

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