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REVIEW

Cruciferous Vegetables, Glutathione S-Transferases, and Implications of Their Interaction to Colorectal Cancer Risk: A Review

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Abstract Globally, colorectal cancer is the third most common type of cancer in men and the second most common in women. As the rate of this cancer increases with the degree of industrialization and urbanization, many researchers emphasize the importance of diets as a decisive factor in the etiology of this cancer. To be specific, the hypothesis that fruit and vegetable intake would act as preventive measurement against colorectal cancer has gained much interest for the general population as well as medical professionals. However, results of epidemiological studies were somewhat inconsistent and showed weak associations in this regard. One possible explanation regarding these controversial results could be due to limited understanding of the interaction between genetic variations and nutrients and their ability to impede cancer development. The objective of this review was to introduce the chemopreventive mechanisms of cruciferous vegetables as well as their active compounds. Furthermore, existing evidence regarding interactions between genetic variations in the key biotransformation enzyme (*i.e.*, glutathione *S*-transferase) and the effect of the intake of cruciferous vegetables against the risk of colorectal cancer were critically discussed.

Keywords cancer prevention · colorectal cancer · cruciferous vegetables · gene-diet interaction · glutathione S-transferases

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Introduction

Cancers are characterized by genomic changes and may be influenced at multiple stages by environmental factors. These factors cannot only help prevent occurrence of this disease but also influence its progression and treatment (Vargas and Thompson, 2012). For example, migrant data has shown that, in populations moved from low-risk to high-risk countries, the cancer mortality (*e.g.*, from colorectal cancer) of migrants eventually reached to that of the adopted country, reinforcing the significance of environmental factors (Grulich et al., 1995). Of cancers, colorectal cancer is the third most common type of cancer in men and the second most common in women. The incidence and mortality of colorectal cancer, similar to those of other cancers, differ significantly depending on factors such as sex, race, and ethnicity (Vargas and Thompson, 2012). Interestingly, as the rate of this cancer increases with the degree of industrialization and urbanization, many researchers emphasize the importance of diets as a decisive factor in the etiology of colorectal cancer (Marshall, 2009).

The hypothesis that fruit and vegetable intake would be preventive against colorectal cancer has gained much interest. In fact, multiple *in vitro*/*in vivo* studies have reported the putative biological mechanisms of the chemoprotective effects of fruits and vegetables (Kassie et al., 2003, Arulselvan et al., 2012). Results of epidemiological studies, however, were somewhat inconsistent and showed weak associations in this regard (Glade, 1999). One of possible explanations regarding these controversial results might be due to the interaction between diets and genes, which has not yet been considered. Furthermore, given the various types of vegetables (and their phytochemicals), as well as interaction between genetic variations and nutrients for chemopreventive benefits, studies stratified by individuals genotypes responsible for metabolizing bioactive compounds; thus exposure levels of fruits and vegetables are warranted. Therefore, the objective of the present review was to report and critically discuss existing evidence regarding interactions between genetic variations in the key biotransformation enzyme (*i.e.*, glutathione *S*-transferase (GST)), and the effect of the intake

Table 1 Cruciferous vegetables, glucosinolates, and ranges thereof

Vegetables	Trivial name	Range	Reference
	Aliphatic glucosinolates		
Red radish	Glucoraphenin	1.6–15.0 (mg/100 g FW)	(Ciska et al., 2000)
Kale	Glucoraphanin	0.6–1.4 (μmol/g DW)	(Kushad et al., 1999)
Brussels sprouts	Sinigrin	3.2–9.1 (μmol/g DW)	(Kushad et al., 1999)
kohlrabi	Glucoerucin	0.0–8.1 (μmol/g DW)	(Park et al., 2012)
Chinese cabbage	Gluconapin	0.3–61.1 (μmol/g DW)	(Kim et al., 2013)
Chinese cabbage	Progoitrin	1.1–5.3 (μmol/g DW)	(Kim et al., 2013)
Turnip	Epiprogoitrin	0.0–0.9 (μmol/g DW)	(Padilla et al., 2007)
Turnip	Gluconapoleiferin	0.0–7.5 (μmol/g DW)	(Padilla et al., 2007)
Rape leaf	Glucoalyssin	0.0–4.0 (μmol/g DW)	(Font et al., 2005)
	Indole glucosinolates		
kohlrabi	Glucobrassicin	0.4–2.9 (μmol/g DW)	(Park et al., 2012)
Broccoli	4-Methoxyglucobrassicin	1.63–1.79 (μmol/g FW)	(Hwang and Kim, 2013)
Broccoli	Neoglucobrassicinc	0.12–0.24 (μmol/g FW)	(Hwang and Kim, 2013)
	Aromatic glucosinolates		
Kerguelen cabbage	Glucotropaeolin	5.4–11.9 (μmol/g DW)	(Barillari et al., 2005)
Broccoli	Gluconasturtiin	0.1–0.9 (μmol/g DW)	(Kushad et al., 1999)

of cruciferous vegetables on the risk of colorectal cancer.

Cruciferous Vegetables, Bio-active Compounds, and Chemopreventive Potential

Cruciferous vegetables, named after their flowers with four equal-sized petals in the shape of a crucifer, are commonly consumed vegetables belonging to the *Brassica* genus, such as cabbage, broccoli, turnip, bok choy, and kohlrabi. Other cruciferous vegetables including wasabi, radish, and watercress, however, do not belong to the *Brassica* genus. Unlike most other vegetables, cruciferous vegetables are unique in that they contain substantial amounts of sulfur compounds, glucosinolates, which are responsible for their pungent taste (Higdon et al., 2007). The health-promoting effects (including cancer prevention) of cruciferous vegetables have been often attributed to glucosinolates. This class of compounds has a basic structure of a β-D-thioglucose, a sulfonated oxime moiety and their side chains. The profiles of these compounds vary depending on the cultivars and growth conditions (Fahey et al., 2001; Holst and Williamson, 2004). Representative vegetable sources, glucosinolate, and their levels are summarized in Table 1.

Glucosinolates can be hydrolyzed to a wide range of bio-active compounds (*e.g.*, isothiocyanates; Fig. 1) and the hydrolysis of glucosinolates are mostly depended on the activity of the enzyme myrosinase, which is physically separated from glucosinolates in plant cells; upon the disruption of plant cells, glucosinolates are released and hydrolyzed into breakdown products (Holst and Williamson, 2004). Hydrolysates formed can be affected by the side chain structure, pH, the presence of metal ions, as well as other protein elements (Bones and Rossiter, 2006). Without the activity of myrosinase, it was also demonstrated that glucosinolates can be degraded by the gut microflora. For instance, several strains of bifidobacterium (*i.e.*, *B. pseudocatenulatum*, *B. adolescentis*, and *B. longum*) have shown the ability to digest glucosinolates, sinigrin, and glucotropaeolin into 3-butenenitrile and phenylacetonitrile. These bifidobacteria strains are known to be responsible for digestive degradation of glucosinolates in the human intestinal tract (Cheng et al., 2004).

As briefly mentioned above, cruciferous vegetables, glucosinolates, and their hydrolysates (*e.g.*, isothiocyanates, indoles, and nitriles) have been hypothesized to elicit anti-cancer properties that may contribute to lower risk for colorectal cancer through multiple mechanisms. (*e.g.*, modulation of detoxification enzymes, anti-

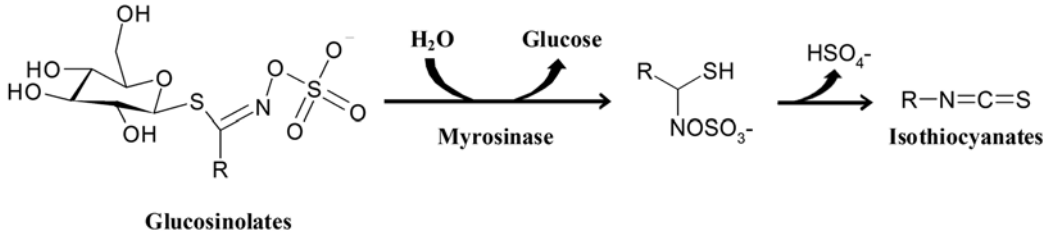

Fig. 1 Hydrolysis of glucosinolates through the myrosinase: isothicyanates production.

Table 2 Chemopreventive mechanisms of cruciferous vegetables and their representative bio-active constituents

Mechanisms of action		Reference
Modulation of carcinogens metabolism	Phase I enzymes modulation	(Skupinska et al., 2009)
	Phase II enzymes modulation	(Abdull Razis et al., 2011)
Anti-proliferation capacity	Apoptosis induction	(Lee et al., 2012)
	Cell cycle arrest	(Hwang and Lee, 2010)
Inhibition of metastasis	Angiogenesis/metastasis inhibition	(Kong et al., 2007)
DNA repair	Induction of DNA repair genes	(Fan et al., 2006)
Anti-oxidative capacity	Inhibition of oxidative DNA damage	(Ferrarini et al., 2011)
Epigenetic modulation	Histone acetyltransferases/deacetyltransferases modulation	(Nian et al., 2009)
	MicroRNA regulation	(Shan et al., 2012)

oxidative effects capacity, and induction of apoptotic cell death; summarized in Table 2). Among them, modulation of biotransformation enzymes and carcinogen metabolism via cruciferous vegetables and their phytochemicals is one of the most widely investigated mechanisms in many animal models of colorectal cancer.

Biotransformation Enzymes: Difensive Mechanism

Living organisms are continuously exposed to foreign chemical species, the so-called xenobiotics. These xenobiotics, which are normally not produced or anticipated in organisms, can interact within the body to exert teratogenic, mutagenic, as well as carcinogenic effects via various mechanisms. Humans have several defensive systems against such xenotoxic compounds. The human body continuously casts off cells that are exposed to these toxic compounds (*e.g.*, surface cells of mouth, esophagus, stomach, and other tissues), activates general detoxifying mechanisms, antioxidative defense (*e.g.*, glutathione transferases), and repairs DNA in response to DNA damage (*e.g.*, DNA adduct) (Mannervik and Danielson, 1988; Ames, 1989; Berwick and Vineis, 2000).

Biotransformation enzymes are a part of the complex defensive systems that play a central role in the metabolism, elimination, and/or detoxification of endogenous and exogenous compounds. In general, the biotransformation process converts lipophilic compounds to polar compounds that are efficiently excreted in the urine. However, in some instances, this transformation leads to the formation of a more reactive metabolite; thus, biotransformation enzymes have both detoxification and activation processes in the body (Meyer, 1996). Despite its complexity, this system can be simplified by dividing it into two general phases (*i.e.*, phase I and phase II biotransformations) based upon the enzymatic actions that occur in each phase. Generally, these enzymatic transformations occur sequentially (Omiecinski et al., 2010).

The reactions of phase I enzymes (*i.e.*, oxidation, reduction, and hydrolysis) are considered as a "preparation step" for the subsequent phase II enzymatic actions. Reactions by appropriate phase I enzymes generate metabolites that are generally more polar than the parent compound; thus, there is less probability of the metabolites penetrating into organs and getting reabsorbed by the kidney. In general, phase I enzymes are located in the endoplasmic reticulum, and the main role of these enzymes is to add a functional group to compounds via oxidation, reduction, and hydrolysis. Through these reactions, primary metabolites can be converted to even more reactive or inactive metabolites, depending upon the structure of the parent compound. In most cases, however, they are conjugated by the phase II enzymes for excretion. Phase II enzymatic reactions include glucuronidation, sulphation, acetylation, and conjugation with glutathione or amino acids (Omiecinski et al., 2010).

Glutathione S-transferases, Cruciferous Vegetables, and Implications of Their Interaction to Cancer Risks: The Current Understanding

Glutathione S-transferases and gene-diet interactions. GSTs are one of the major classes of phase II enzymes. In humans, eight distinct gene families encode these soluble GSTs, namely, and GST alpha on chromosome 6, GST mu on chromosome 1, GST theta on chromosome 22, GST pi on chromosome 11, GST zeta on chromosome 14, GST sigma on chromosome 4, GST kappa on an unknown chromosomal location, and GST chi on chromosome 10 (Strange et al., 2001). These enzymes are cytosolic membrane-bound enzymes that are involved in the detoxification of electrophilic compounds (*e.g.*, carcinogen and drugs) and metabolites of oxidative stress via conjugation of glutathione, allowing protection of some tissues from somatic mutations in DNA (Rebbeck, 1997; Mo et al., 2009). GSTs also have a function in DNA repair, wherein they regulate the induction of certain proteins and enzymes (Rebbeck, 1997).

Several studies have been conducted on the association of cancers and the genetic variations of GSTs; of these variations, polymorphisms in GST mu (GSTM), GST theta (GSTT), and GST pi (GSTP) have been intensively investigated. As a result, it is widely accepted that the variation in the ability to detoxify or deactivate carcinogens due to such polymorphic variations in GSTs can result in "*inter-individual genetic differences in cancer susceptibility*" (Rossini et al., 2007). In addition, environmental

factors (*e.g.*, diets) are also known to interact with these genes to manifest and modify the risk of colorectal cancers (Gertig et al., 1998; Reszka et al., 2006), This might occur, because phytochemicals, including isothiocyanates, from cruciferous vegetables are also metabolized as xenobiotics via biotransformation enzymatic reactions (Lampe, 2009). Therefore, genetic variations in GSTs may also affect the metabolism of compounds from fruits and vegetables, indicating that the length of exposure of either xenobiotics (*e.g.*, carcinogens) or beneficial compounds from cruciferous vegetables can be influenced by individual genotypes of biotransformation enzymes in a similar manner.

Existing evidence: A critical evaluation. Yang et al. (2010) investigated the association between isothiocyanates and genetic variations of GSTs regarding its potential modifying effects on the risk of colorectal cancer. The authors assessed the dietary intake of cruciferous vegetables, such as Chinese greens, green cabbage, Chinese cabbage, cauliflower, white turnip/radish, and the pre-diagnostic measurements of urinary isothiocyanates, using a nested case control study of the Shanghai Women's Health Study. This large-scale population-based cohort study included 75,049 Chinese women aged 40–70 years during the years 1997 to 2000 from seven different urban communities of Shanghai. Subjects habitually consumed cruciferous vegetables had a low incidence of colorectal cancer. Thus, the above mentioned the authors (Yang et al., 2010) addressed that the concentrations of urinary isothiocyanates were inversely associated with the risk of colorectal cancer. More specifically, there was a statistically significant inverse association in the GSTM1-null group (p =0.04), and nearly significant association in the GSTP1-null group (p =0.07). The strongest inverse association (p =0.03) was found in the group with both GSTM1-null and GSTP1-null genotypes. However, no apparent associations were found between dietary cruciferous vegetable intake and the risk of colorectal cancer in all of the GST genotypes.

The major finding of this study was the inverse association between levels of isothiocyanate and the risk of colorectal cancer based upon the individual genotype of biotransformation enzymes; the metabolic exposure of isothiocyanates differed by GST genotypes rather than by individual dietary intake. These findings may be attributed to a less efficient metabolism in the GST-null group, allowing them to be exposed to isothiocyanates for a longer period of time compared to others, and beneficial in terms of reducing the risk of colorectal cancer. A possible mechanism of this protective effect is that isothiocyanates may modulate the activity of the enzymes involved in carcinogen metabolism, especially in the induction of phase II enzymes (Talalay and Fahey, 2001; Krajka-Kuzniak et al., 2010). On the other hand, it is worthwhile to note that Vogtmann et al. (2014) recently tested the interaction between cruciferous vegetables and GST genotypes using incidence density sampling in the Shanghai Men's Health Study, which is interesting because these two studies were tested with the same hypothesis in an identical ethnic background. In their studies, colorectal cancer cases were matched with non-cases, and cruciferous vegetable intake was then assessed using food frequency questionnaire as well as urinary isothiocyanate levels. As a result, they found no evidence supporting the involvement of cruciferous vegetable intake as well as GST genotypes in relation to colorectal cancer, which is in contrast to the report of Yang et al. (2010) as well as conventionally accepted chemoprotective potential of cruciferous vegetables. The authors explained that such differences could be related to sex differences and/or prevalence of other risk factors such as smoking. Thus, future investigations warrant considering putative interaction between smoking and GST gene polymorphisms on a population level (Vogtmann et al., 2014).

Yang et al. (2010) recruited an exceptionally large number of subjects and completed a baseline survey that included all information in great detail. In addition, cases of colorectal cancer and controls were matched individually with reasonable criteria, and most of the important factors were accounted for. These criteria included age (±2 years) at base line, date (<30 days) and time (morning or afternoon) of sample collection, menopausal status (before or after), and antibiotic usages (yes or no). Based on these criteria, a total of 1,258 subjects were selected for the control group. The authors also performed blind control-laboratory analyses to avoid individual bias. However, there are limitations in this study as well. First, the food questionnaire may not demonstrate accurate amount of food intake expected; this might explain the weak correlation between urinary excretion of isothiocyanates and cruciferous intake in the studies of Yang et al. (2010) and Fowke et al. (2001). Moreover, because the authors also mentioned, the amount of "actual" isothiocyanates metabolized in our body could vary considerably depending upon several other unaccounted/confounding factors such as species of cruciferae, maturity, growth conditions, and cooking processes. Lastly, while knowing that GSTs are key enzymes for the metabolism of isothiocyanates (12), any explanation about the possible role of other biotransformation metabolism enzymes or important factors in terms of cancer risk (*e.g.*, cytochrome P450) (Northwood et al., 2010) were not considered in the study of Yang et al. (2010) , except for GSTM1 and GSTT1. Despite the limitations mentioned above, the results from the present study provided evidence of a possible association between dietary isothiocyanates and the genotype of biotransformation enzymes, including GSTs, with regard to the risk of colorectal cancer.

Epplein et al. (2009) also examined the associations among cruciferous vegetables to GST polymorphisms and colorectal cancer risk. The study population was comprised of subjects from the Multiethnic Cohort Study (n =21,500; multiple ethnicity including African Americans, native Hawaiians, Japanese Americans, Latinos, and Caucasians), who were diagnosed with colorectal cancer. The participants completed a baseline questionnaire that included information on dietary intake of cruciferous vegetables as well as family history, individual medical records, lifestyle, smoking history, body mass index, and alcohol usage. Of the eligible colorectal cancer cases (n =263) and control cases

(n =526), 90 cancer cases and 213 control cases were excluded due to incomplete or missing information, samples, and matching criteria.

A detectable amount of isothiocyanates was found to be inversely related with the risk of colorectal cancer (approximately 41% reduction), whereas no dose-dependent association was found between the amount of isothiocyanates ingested and the incidence of colorectal cancer. Although there was a weak suggestion that for individuals with the AG or GG genotype of GSTP1, a detectable amount of urinary isothiocyanates decreases colorectal cancer risk compared to those with GSTP1 AA genotype, the interaction was on the borderline of statistical significance (p =0.09 for interaction of isothiocyanates with GSTP1 polymorphism).

Results of the present study also support the notion of an inverse association between the level of isothiocyanates and the risk of colorectal cancer and provide evidence for the interactions among GST genotypes, cruciferous vegetables, and colorectal cancer risk; however, there is also inconsistent finding compared to other studies. To be specific, Epplein et al. (2009) found that there was a positive relationship between GSTM1-null and the risk of colorectal cancer, in contrast to the relationship reported by other studies (Slattery et al., 2000; Yang et al., 2010). This finding could be explained by a relatively small number of cases and controls. The authors also attempted to analyze the interaction between the risk of colorectal cancer and individuals with a homozygous deletion of both GSTM1 and GSTT1; however, the risk estimates were not reported due to the small sample size, which could have been rectified by recruiting more subjects from the population. Another issue of the present study is that the dietary consumption of cruciferous vegetables was not performed at a sufficient level (*i.e.*, the level of urinary isothiocyanates was insufficient to be detected); as a result, nearly 50% of cases and controls were excluded from the statistical analysis for comparison of the risk of colorectal cancer and the isothiocyanate level. Among the study population, Japanese American subjects showed the largest intake of cruciferous vegetables; however, it was still only about 60% of that reported in the Shanghai Chinese Study (Epplein et al., 2009; Yang et al., 2010). In addition, the time interval between sample collection and diagnosis of cancer was relatively short (*i.e.*, 1.4 years) as compared to that in other studies. A significant association of isothiocyanates was found only from subjects whose samples were collected for 10 years or more prior to the diagnosis, and this inverse relationship became stronger with a longer follow-up period (Moy et al., 2008). Collectively, the results of the present study were added to the evidence, indicating beneficial effects of ingesting cruciferous vegetable against the risk of colorectal cancer. However, further investigation with a larger sample size and longer follow-up is required.

Lastly, Seow et al. (2002) examined the association between dietary isothiocyanates and their interactions with the GSTs (*i.e.*, GSTM1, GSTT1, and GSTP1) and the risk of colorectal cancer in a Singapore Chinese population (Seow et al., 2002). Colorectal cancer cases were retrieved from the Singapore Chinese Health Study, a population-based, prospective investigation of diet and cancer risk (Hankin et al., 2001). In this nested case-control study, the authors identified 213 cases with 1,194 controls. Dietary intake of isothiocyanates was computed based on information collected via a semi-quantitative food-frequency questionnaire on the amount of intake of cruciferous vegetables. Nine cruciferous vegetables were included in the questionnaire for the study: Chinese white cabbage, Chinese mustard, Chinese flowering cabbage, watercress, Chinese kale, head cabbage, celery cabbage, broccoli, and cauliflower. The subjects were then categorized into either a “high” intake group (*i.e.*, a group consuming more cruciferous vegetables than the median amount) or a “low” intake group (*i.e.*, a group consuming less cruciferous vegetables than the median amount). In addition, genotypes of GSTs (*i.e.*, GSTM1, GSTP1, and GSTT1) were analyzed from peripheral blood lymphocytes or the buccal mucosa. The authors found that a high intake of isothiocyanates was associated with a reduced risk of colorectal cancer; however such an association was not found to be statistically significant (odds ratio, 0.81; 95% confidence interval, 0.59–1.12). Although there were no overall associations between the genotypes of GSTs and the risk of colorectal cancer, it was observed that subjects with GSTM1 and GSTT1-null genotypes showed a 57% reduced risk of colorectal cancer in the high-intake group as compared to that in the low-intake group (odds ratio, 0.43; 95% confidence interval, 0.20–0.96). Interestingly, there was a significant risk reduction in colon cancer (odds ratio, 0.31; 95% confidence interval, 0.12–0.84), whereas were not affected in rectal cancers. One of the major findings of the present study was that the authors demonstrated a significant inverse correlation between the intake of cruciferous vegetables and the risk of colorectal cancer among GSTM1 and GSTT1-null individuals. This finding is also in agreement with similar studies (Lin et al., 1998; Yang et al., 2010). However, although the authors discussed that the collection of dietary information using a validated questionnaire is one of the strengths of their study, it is not always possible to demonstrate the accurate amount of food intake, as discussed earlier. In addition, sufficient information was not available regarding their criteria for selecting controls from the study population. Moreover, as addressed in the present study, the follow-up period for each subject was only five years, which is a relatively short period of time. Taken together, the results of the present study supported the notion that high intake of bioactive components from cruciferous vegetables is inversely associated with the risk of colorectal cancer. Such effects were significantly pronounced in GSTM1- and GSTT1-null individuals, in whom isothiocyanates from cruciferous vegetables are metabolized or excreted more slowly.

Conclusions and Future Directions

Genetic variations of detoxification enzymes are one of the most important factors that influence the risk of cancer and other diseases, because these enzymes play a crucial role in protection against both endogenous and exogenous toxic compounds. Although a number of observational studies, including studies discussed above, have been performed regarding the effect of genetic variations in GSTs and the dietary intake of cruciferous vegetables in the risk of colorectal cancer; however, results from these studies are somewhat discrepant and not statistically significant. For example, Steck et al. (2007) assessed whether GST genotypes (*i.e.*, GSTM1, GSTT1, GSTP1, and GSTA1) are associated with urinary isothiocyanates metabolites and a known dose of broccoli as a source of glucosinolates. The authors found that GSTM1-null individuals showed higher urinary excretion (62%) of isothiocyanates than GSTM1 individuals (39%; p =0.03). These unexpected results indicate the possibility of an alternative pathway for isothiocyanate metabolism. Other studies have found an inconsistent association between GSTs and the risk of colorectal cancer from different populations (Butler et al., 2001; Kiss et al., 2004; Yeh et al., 2007).

The discrepancies in the results may be because 1) cancer risk, particularly colorectal cancer, is determined by the presence of a number of environmental factors such as carcinogens, radiation, infections, and diet, (Thompson and Gerner, 2009), 2) the variations in the actual intake of isothiocyanates depending upon factors such as the cooking process and the conditions of vegetables have recently become common to directly measure urinary isothiocyanate levels instead of assessing the food-frequency questionnaire to avoid the subject-introduced bias, and 3) although the role of GSTs was focused on the detoxification processes. It is also known that GSTs can non-catalytically bind to numerous ligands for nuclear hormone receptors (Listowsky et al., 1988); thus, it is possible that genetic variations on GSTs may have other consequences beyond xenobiotic metabolism. To conclude, it appears reasonable to believe that certain cruciferous vegetables and their bioactive compounds may have beneficial effects on the risk of colorectal cancer. Although it remains unclear as to how individuals with different genetic variations affecting detoxification enzymes (*e.g.*, GSTs) are affected by various environmental factors. To elucidate such interactions between dietary active components and genetic variations (not limited to GSTs), and to provide adequate statistical power, further studies with larger sample sizes with the analyses of genetic variations in responsible pathways are warranted.

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