Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2009 January ; 18(1): 184–195. doi:10.1158/1055-9965.EPI-08-0710.

Cruciferous vegetable consumption and lung cancer risk: a systematic review

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Abstract

Background—Cruciferous vegetables, rich in isothiocyanates, may protect against lung cancer. Glutathione S-transferases are important in metabolizing isothiocyanates; hence, variants in *GST* genes may modify the association between cruciferous vegetable intake and lung cancer. We carried out a systematic review to characterize the association between cruciferous vegetable intake and lung cancer risk, with an emphasis on the potential interaction between cruciferous vegetables and *GST* gene variants.

Methods—A search of the epidemiological literature through December, 2007 was conducted using 15 bibliographic databases without language restrictions. Thirty-one studies on the association between lung cancer and either total cruciferous vegetable consumption (6 cohort and 13 case-control studies) or specific cruciferous vegetables (1 cohort and 11 case-control studies) were included.

Results—We ascertained 31 studies of either total cruciferous vegetable consumption (6 cohort,13 case-control studies) or specific cruciferous vegetables (1 cohort, 11 case-control studies) in relation to lung cancer risk. The risk of lung cancer among those in the highest category of total cruciferous vegetable intake was 23% lower in case-control studies (random-effects pooled odds ratio 0.77; 95% CI 0.68-0.88) and 17% lower in cohort studies (pooled relative risk 0.83; 95% CI 0.62-1.08) compared to those in the lowest category of intake. The strongest inverse association of total cruciferous vegetable intake with lung cancer risk was seen among individuals with *GSTM1* and *GSTT1* double null genotypes (OR 0.41; 95% CI 0.26-0.65).

Conclusions—Epidemiologic evidence suggests that cruciferous vegetable intake may be weakly and inversely associated with lung cancer risk. Due to a gene-diet interaction, the strongest inverse association was among those with homozygous deletion for *GSTM1* and *GSTT1*.

INTRODUCTION

Lung cancer is the leading worldwide cause of cancer death (1). Cigarette smoking accounts for approximately 85% of the population burden of lung cancer in developed countries such

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as the United States, but selected dietary factors may modulate lung cancer risk (2). A major report of the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) concluded that the evidence was “limited—suggestive” that vegetable intake is inversely associated with lung cancer (3). However, the associations with lung cancer may vary according to the specific class of vegetable considered.

In particular, cruciferous vegetables (broccoli, cabbage, cauliflower, Brussels sprouts, kale) have been hypothesized to have anti-cancer properties that may contribute to reduced risk of lung cancer. Cruciferous vegetables are a rich source of isothiocyanates. Isothiocyanates may inhibit the bioactivation of procarcinogens found in tobacco smoke such as polycyclic aromatic hydrocarbons. Isothiocyanates may also enhance excretion of carcinogens before they can damage DNA (4,5). Sulforaphane, a major isothiocyanate found in broccoli, can induce cell cycle arrest and apoptosis (5,6).

GSTM1 and GSTT1, two Phase II enzymes encoded by two genes belonging to the Glutathione S-transferase (GST) family (6) play an important role in isothiocyanate metabolism (7). A common polymorphism in both the *GSTM1* and *GSTT1* genes results in gene deletion, and individuals with homozygous deletions are devoid of the respective enzyme activity (6). Individuals with homozygous deletion of *GSTM1*, *GSTT1*, or both, may metabolize isothiocyanates less efficiently and may be more intensely exposed to them after consumption of cruciferous vegetables. For this reason, individuals with the null *GSTM1* or *GSTT1* genotypes may have a lower risk of lung cancer when exposed to isothiocyanates (8-10).

Several epidemiological studies have assessed the association between cruciferous vegetable intake and lung cancer, but no systematic reviews are available to thoroughly unify this information. To address this information gap, we performed a meta-analysis of the evidence on this topic, including the potential gene-dietary interaction between cruciferous vegetable intake and *GST* genotypes.

METHODS

This systematic review stemmed from a project funded by the WCRF/AICR to develop a report entitled `Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective' (3). All work adhered to a standardized protocol developed by WCRF (http://www.wcrf.org/research/second_wcrf_aicr_report.lasso) (2). The WCRF report did not specifically consider the topic of cruciferous vegetables and lung cancer risk.

Search strategy

For the WCRF report, we sought all evidence on the associations between dietary intake, physical activity, or anthropometric measures and lung cancer that were reported in randomized clinical trials, cohort studies, and case-control studies. We used the search strategy for dietary factors as previously in (11), adapted for the outcome of lung carcinoma as described in (12). The following electronic databases were searched: PubMed, Embase, Pascal, ISI Web of Science, the Cochrane Library, Biological Abstracts, Cumulative Index to Nursing and Allied Health Literature, National Institute on Alcohol Abuse and Alcoholism (NIAAA)-Alcohol and Alcohol Problems Science Database, Agricola, CINAHL-EBSCOhost, Index Medicus for WHO Eastern Mediterranean Region, Index Medicus for South East Asian Region, and Latin American and Caribbean Center on Health Sciences Information. The search included all studies published up to April 2006. We also hand-searched references in the relevant review articles from the bibliographic database search and those cited in the 1997 WCRF report (2) or chosen for data abstraction. After the original WCRF search, we extended the PubMed search through December 2007. There were no language restrictions. If a published article was in a

language that was beyond the expertise of our research team, WCRF had the article (13) translated into English.

Study Selection

The following exclusion criteria were applied to the screening of articles for the WCRF report: 1) no original data (reviews, editorials, meta-analyses); 2) studies not addressing the association between dietary intake, physical activity, or anthropometric measures and lung cancer; 3) studies not in humans; and 4) case reports and case series. The eligibility of each abstract or full-text article was assessed independently by two reviewers.

For the present report, we further limited the studies to those that reported on the association between cruciferous vegetable intake and lung cancer. Cruciferous vegetables were measured in different ways, including: 1) total cruciferous vegetable intake, 2) total isothiocyanate intake, and 3) intake of specific individual cruciferous vegetables (e.g. broccoli, cabbage, or cauliflower). When measures of association or variability were not reported or could not be calculated using the data provided, we excluded the papers from the formal meta-analysis but discussed the findings of the paper qualitatively. We made no systematic effort to contact authors. If separate reports from the same study were published, the report with the most updated data was selected for inclusion.

Data abstraction—For each eligible article, two reviewers abstracted the data into an electronic database created by WCRF. The data abstraction was performed serially, with any disagreements between reviewers resolved by consensus. Each reviewer classified the vegetables studied in each paper into classes (e.g. cruciferous vegetables, allium vegetables) according to the WCRF protocol (2). If a specific vegetable was not listed in the protocol, a nutritionist [LEC] assigned the appropriate vegetable subgroup. In the WCRF protocol, broccoli, cabbage, turnip/mustard greens, kale, sauerkraut, and cauliflower were classified as cruciferous vegetables. To assess study quality, we adapted the criteria used by Longnecker *et al*(14) for observational studies.

Statistical analysis

The primary quantitative analyses focused on total dietary intake of cruciferous vegetables. Total cruciferous vegetable consumption was typically defined as a combination of at least 3 cruciferous vegetables (15), which usually included broccoli and cabbage plus other cruciferous vegetables. We also analysed the associations between specific cruciferous vegetables and lung cancer risk. Separate meta-analyses were conducted for case-control and prospective cohort studies, by smoking status (never smokers or ever smokers) and by ethnicity (Western or Asian).

For all studies, odds ratios (OR) or relative risks (RR) and their respective 95% confidence intervals (95% CI) were abstracted. When a study reported several relative risk estimates, we abstracted the one adjusted for the most covariates. For studies that did not report estimates (16-18), we calculated the unadjusted ORs and 95% CIs based on published data. Pooled OR and RR estimates were obtained using inverse-variance weights in random effects models. Statistical heterogeneity was assessed using the DerSimonian and Laird's Q statistic and the I^2 statistic.

Sensitivity analyses to examine the influence of each individual study were conducted by excluding each study from the meta-analysis and comparing the point estimates including and excluding the study. Meta-regression was used to explore for sources of heterogeneity. Publication bias was examined using funnel plots.

When sufficient data were presented in the original publication (≥3 exposure categories of intake frequency along with the numbers of cases and controls within each category), we assessed for the presence of a dose-response trend (19), To assess for interaction between GST genotypes and cruciferous vegetable intake on the risk of lung cancer, we estimated the association between total cruciferous vegetable intake and lung cancer stratified by *GSTM1* and *GSTT1* status. With the exception of one cohort study (20) which used a genotyping assay that could differentiate between three *GSTM1* and *GSTT1* genotypes of, two possible genotypes (present and null) were reported for *GSTM1* and *GSTT1* in all case-control studies. Data analyses were thus stratified as follows: *GSTM1* present or null, *GSTT1* present or null, and *GSTM1/GSTT1* double present or double null. We tested for within-study effect modification by *GST* genotype by calculating the difference in (log) odds ratios between *GST* subgroups within each study (21,22). We then obtained a summary interaction ORs by pooling these differences across studies.

RESULTS

Search results

We identified 37 studies that quantified the association between cruciferous vegetable consumption and lung cancer risk (Figure 1). Of these, we excluded two early reports from studies that subsequently published updated data (23,24), two that reported on individual cruciferous vegetables but did not report the total number of cases (25,26), one that reported on interaction between cruciferous vegetables and *GST* genes reported genotyping data that were not comparable and did not provide sufficient data to calculate standard errors to be included in the meta-analysis (20), and one that reported only on a biomarker (rather than dietary intake) of isothiocyanates (8). Of the 31 studies included in the meta-analyses, 19 studies (6 cohort (15,27-30) and 13 case-control (13,16-18,31-39)) reported on total cruciferous vegetable intake. One cohort study (40) and 11 case-control studies (41-51) reported on intake of individual cruciferous vegetables. Quality assessment for the studies reported on total cruciferous consumption and lung cancer is summarized in Appendix 1.

Total cruciferous vegetables

Six prospective cohort studies (Table 1) and 13 case-control studies (Table 2), representing a total of 8227 lung cancer cases, reported associations between total cruciferous vegetable intake and lung cancer risk. The studies were carried out in Europe (8 studies (13,27,28,32, 34,36-38)), the United States (6 studies (15,16,18,29,30)), Asia (3 studies (17,31,35)), Canada (1 study (39)), and Australia (1 study (33)). The duration of follow-up ranged from 4-12 years in the six prospective cohort studies (15,27-30). All prospective studies adjusted for smoking status. Of the 13 case-control studies, five were confined to never smokers (31,34,36,38,39) Of the eight studies that included ever smokers, five reported ORs adjusted for smoking (13, 32,33,35,37).

Compared to those in the lowest categories of total cruciferous vegetable intake, the risk of lung cancer among those in the highest consumption categories was 23% lower (random-effects pooled odds ratio 0.77; 95% CI 0.68-0.88; p heterogeneity = 0.31; I^2=13.8%) in case- control studies and 17% lower in cohort studies (pooled relative risk 0.83; 95% CI: 0.62-1.08; p heterogeneity = 0.02; I^2 = 62.8%) (Figure 2). For case-control studies, the results did not substantially differ when the meta-analysis was restricted to studies from never smokers (31, 32,34-39) (pooled OR: 0.79; 95% CI: 0.64-0.97; p heterogeneity 0.48; I^2=0%).

All prospective cohort and 10 case-control studies reported at least three categories of total cruciferous vegetable intake (Table 3). Of the 6 prospective cohort studies, 3 studies were compatible with an inverse dose-response association between cruciferous vegetable intake

and lung cancer risk (28-30), whereas three others showed no evidence of a dose-response trend (15,27,30). Eight case-control studies provided dose-response data in sufficient detail to be included in dose-response meta-analysis. The pooled OR for lung cancer associated with an increase of one cruciferous vegetable serving per day was 0.74 (95% CI: 0.73-0.75). Two additional case-control studies (18,32) reported frequency of intake (i.e. low, medium, high) that could not be combined with the other studies. Of the two studies, one (32) was compatible with a decrease in lung cancer risk with increasing consumption of cruciferous vegetables whereas the other (18) showed no apparent trend.

Broccoli and cabbage as individual cruciferous vegetables were also inversely associated with lung cancer risk. In data generated from case-control studies, the pooled odds ratios for lung cancer risk comparing the highest-versus-lowest categories of intake were 0.53 (95% CI: 0.34-0.83; p heterogeneity = 0.14; I^2 = 43.0%) for broccoli (39,42,44-46) and 0.70 (95% CI: 0.54-0.91; p heterogeneity = 0.02; I^2=54.9%) for cabbage (37,39-41,43,48-51).

Results stratified by *GST* genotypes

Five case-control studies (16,35-37,52) (N=3,715 lung cancer cases) reported on the association between cruciferous vegetable consumption and lung cancer risk stratified by *GSTM1* and/or *GSTT1* genotypes (Table 4). Of these, one reported only on *GSTM1* (36), whereas four assessed both *GSTM1* and *GSTT1* (16,18,35,37). Cruciferous vegetable consumption was measured by food frequency questionnaire in all 5 studies, and exposure was quantified either as intake of isothiocyanates (n=2 studies (16,36)) or of total cruciferous vegetables (n=3 studies (18,35,37)).

In these 5 studies, the pooled OR of lung cancer for the highest-versus-lowest category of cruciferous vegetable intake was 0.74 (95% CI: 0.66-0.84) (Figure 3). When stratified by genotype, the inverse association between cruciferous vegetable intake and lung cancer was stronger in those who were null for both *GSTM1* and *GSTT1* (pooled OR: 0.41; 95% CI: 0.26-0.65; p heterogeneity=0.64; I^2= 0) than in those with the *GSTM1* and *GSTT1* present genotype (OR: 0.75; 95% CI: 0.62-0.91; p heterogeneity=0.43; I^2= 0). This gene-diet interaction was statistically significant (OR 0.48; 95% CI: 0.28-0.84).

Heterogeneity and publication bias

Meta-regression results showed that study size, geographic location, or gender could not explain the observed heterogeneity for cohort studies. Sensitivity analysis results showed that the exclusion of individual studies did not substantially alter the pooled relative risks, which ranged from 0.75 to 0.91. All funnel plots to assess for possible indication of publication bias for meta-analyses of cohort and case-control studies, in addition to subgroup analyses by *GST* status, appear symmetrical (data not shown).

DISCUSSION

In our systematic review, which included 19 studies of the association between total cruciferous vegetable intake and lung cancer, we found a modest inverse association between cruciferous vegetable intake and lung cancer risk. Compared to those who consumed the least amount of cruciferous vegetables, the risk of lung cancer among those who consumed the most cruciferous vegetables was 23% lower in case-control studies (statistically significant) and 17% lower in prospective cohort studies (not statistically significant). Furthermore, case-control studies showed a significant inverse dose-response trend, although cohort studies provided only equivocal support for the presence of a dose-response trend. Intake of individual cruciferous vegetables (12 studies), such as broccoli and cabbage, was also inversely associated with lung

cancer risk. These associations could not be explained by lack of adjustment for smoking in the original studies.

The summary estimates for case-control and cohort studies both provide evidence of an inverse association between cruciferous vegetable intake and lung cancer risk, but the association seen in cohort studies was slightly weaker and was not statistically significant. This may in part be due to the heterogeneity observed among the prospective cohort studies. A possible source of the heterogeneity in cohort studies may be the diverse populations studied. Of the six cohort studies, four were from the United States, and many of these were of unique study populations, such as white male life-insurance holders (15), health professionals (30), and asbestos-exposed, heavy smokers (29). The levels of cruciferous vegetable intake, along with the prevalence of lung cancer risk factors, would be expected to range widely across these study populations. This could have introduced heterogeneity and attenuated the summary relative risk.

A unique characteristic of cruciferous vegetables is that they are a rich source of glucosinolates (53). The anti-carcinogenic properties of cruciferous vegetables may be attributable to isothiocyanates derived specifically from glucosinolates (53,54). Several experimental and mechanistic studies support a potential anti-cancer role of isothiocyanates (55,56). Sulforaphane, an isothiocyanate found in broccoli, is involved in several pathways including induction of detoxifying genes, cell cycle control, and apoptosis; acting as an antioxidant (56), and inhibiting histone deacetylase (57). These experimental findings buttress the biologic plausibility of the association between cruciferous vegetable intake and lung cancer risk. However, the epidemiologic evidence considered in this systematic review does not allow inferences to pinpoint isothiocyanates as the key protective constituent of cruciferous vegetables as other nutrients and phytochemicals (e.g. folate, flavonols, and carotenoids) found in cruciferous vegetables may also be responsible for the protection against lung cancer.

Genetic factors related to isothiocyanate metabolism have been hypothesized to contribute to inter-individual differences in the degree of protection conferred by cruciferous vegetable consumption (58). Specifically, individuals with *GSTM1* and *GSTT1* null genotypes metabolize isothiocyanates less efficiently, permitting isothiocyanates to remain biologically active for a longer period (58,59). In our meta-analysis, a gene-diet interaction was present; when stratified by *GSTM1* and *GSTT1* variants, the inverse associations between cruciferous vegetable intake and lung cancer risk were more marked in those with the double null genotype. Corroborative findings were also reported in a nested case-control study carried out in China, in which the significant inverse association between urinary isothiocyanate levels and lung cancer risk was stronger among men with the *GSTM1* and *GSTT1* double null genotype (8). The only cohort study (20) to report on the potential interaction between cruciferous vegetables and *GSTM1* on lung cancer risk only presented partial results in the manuscript text, so could not be included in the formal meta-analyses, found no statistically significant interaction not for individuals with one functional allele or homozygous deletion (i.e. null). The presence of a potential gene-diet interaction adds internal consistency to the overall body of evidence on the association between cruciferous vegetables and lung cancer, and takes a step toward addressing the causal criteria of biologic plausibility and coherence. The genotype prevalences for *GSTM1* and *GSTT1* homozygous deletion vary by race/ethnicity but range from 42-60% and 24-51%, respectively (60), making this an important question to resolve due its public health relevance.

Any consideration of a dietary factor in relation to lung cancer needs to carefully evaluate the potential confounding role of cigarette smoking. Cigarette smoking is the principal cause of lung cancer and cigarette smokers tend to eat less healthful diets than nonsmokers (61). Thus, even studies that statistically adjusted for cigarette smoking may show associations due to residual confounding (62). The inverse association between cruciferous vegetable intake and

lung cancer, however, was similar in studies limited to never smokers. Furthermore, residual confounding by smoking is unlikely to explain the interaction between cruciferous vegetable intake and *GST* genotypes. A weakness of the evidence that comprises this systematic review is the measurement error inherent in the use of dietary questionnaires; in the retrospective case-control studies, the potential for recall bias due to cases and controls differential recall of dietary habits is a particular concern (63). Furthermore, the association between cruciferous vegetables and lung cancer may differ depending on whether the vegetables are consumed raw or cooked, because this influences the bioavailability of isothiocyanates (64). The lack of information about cooking methods is thus a potential source of heterogeneity in the results.

In this systematic review, higher intake of cruciferous vegetables was modestly inversely associated with lung cancer risk. The inverse association was stronger among individuals with the null genotype for both *GSTM1* and *GSTT1*. Compared to case-control studies, the associations observed in cohort studies were weaker, were not statistically significant, and had more heterogeneity. Furthermore, the evidence for the gene-diet interaction is based only on case-control data. Consequently, additional cohort data are needed to help understand the lack of consistency in prospective studies and to provide a more precise estimate of the interaction between cruciferous vegetable intake and *GST* genotype.

Acknowledgments

Funding: This research was primarily funded by the World Cancer Research Fund. This report was reviewed by the funding source prior to submission (with no substantive changes), but is independent of the funding source.

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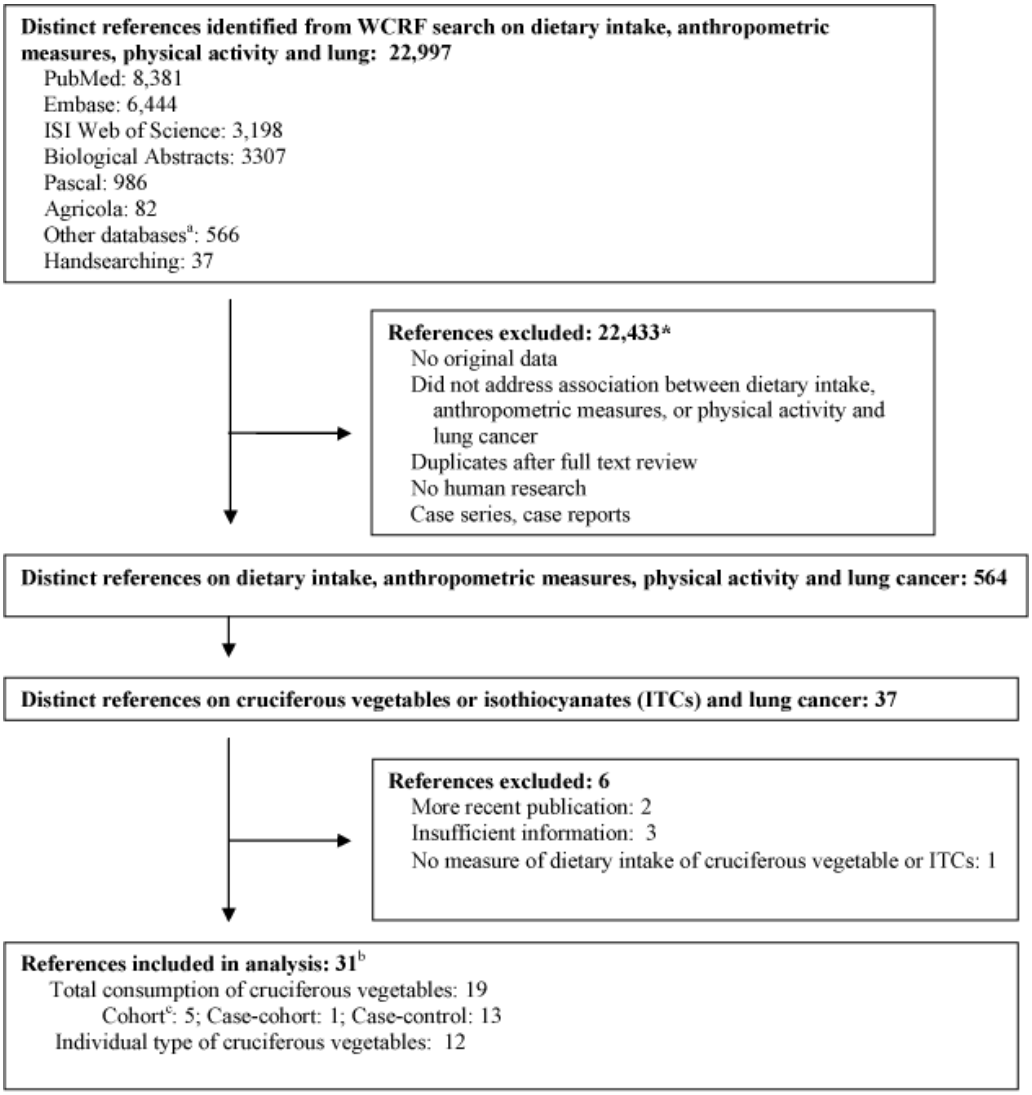

[a]Other databases: NIAAA Alcohol and Alcohol Problems Science Database (n = 48), Cochrane Library (n = 101), CINAHL-EBSCOhost (n = 270), Index Medicus for WHO Eastern Mediterranean Region (n = 4), Index Medicus for South East Asian Region (n = 29), and Latin American and Caribbean Center on Health Sciences Information (n = 114)
[b]Included two relevant references resulted from the update PubMed search through December 2007 (Linseisen(40) and Galeone(51))
[c]One reference included 2 distinct cohort studies (Feskanich(30))
*3 articles not reviewed due to copyright restrictions

Figure 1.
Study selection process

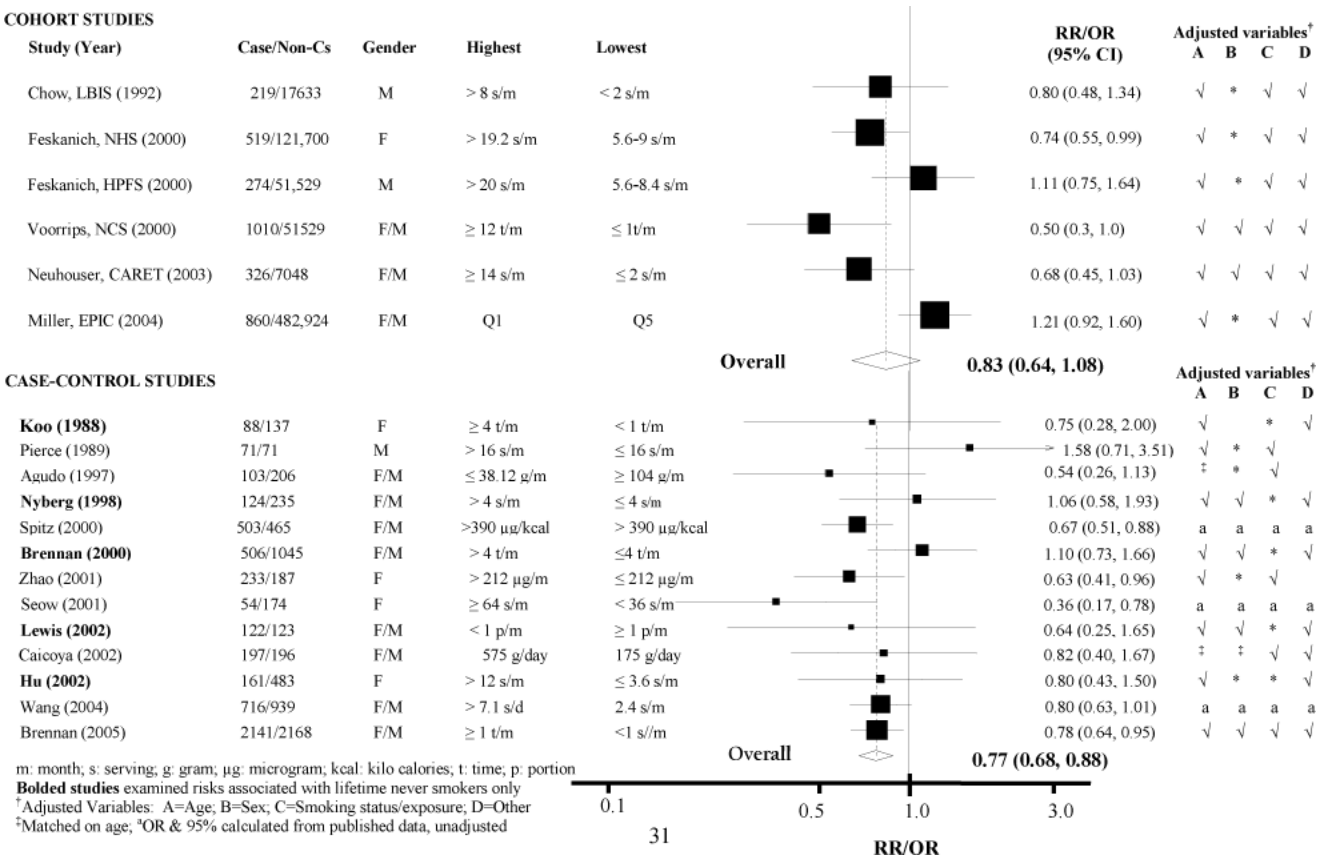

Figure 2.

Forest plot of highest-versus-lowest category of total cruciferous vegetable/ITC consumption and lung cancer risk in cohort and case-control studies

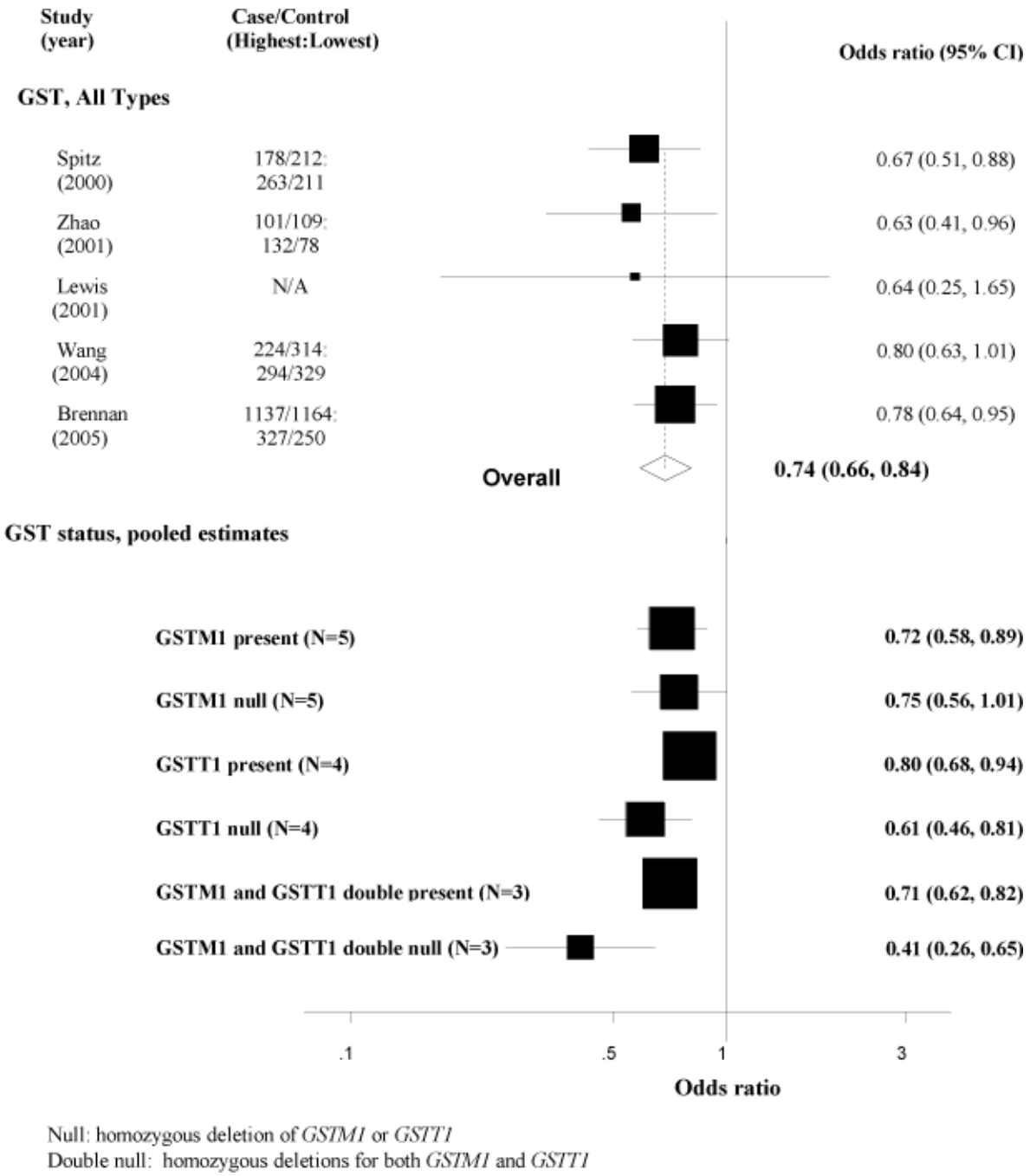

Figure 3.
Forest plot of highest-versus-lowest category of total cruciferous vegetable/ITC consumption and lung cancer risk in case-control studies, stratified by *GSTM1* and *GSTT1* genotypes.

■ Yes; □ No; - Not Applicable; *=Not reported/Unknown	Prospective cohort studies						Case-control studies												
Reference number:	(15)	(27)	(28)	(29)	(30)	(30)	(16)	(35)	(36)	(37)	(18)	(13)	(31)	(33)	(38)	(34)	(32)	(17)	(39)
All observational studies																			
Exposure was assessed at the individual level	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Contributing lung cancer cases were histologically/pathologically confirmed in at least 90% of the cases?	*	□	■	■	■	■	■	■	■	*	■	■	■	■	□	■	■	■	■
The authors control for potential confounding risk factors (e.g. age, sex) to lung cancer or effect modification by genetic variants and, *if applicable*, smoking history (e.g. smoking status, pack-years, duration of smoking)	■	■	*	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Dietary questionnaire used was validated	*	*	■	■	■	■	■	■	*	*	■	■	*	□	*	*	*	*	■
All prospective studies																			
Loss of follow-up was independent of exposure	*	*	*	*	*	*	-	-	-	-	-	-	-	-	-	-	-	-	-
All case-control studies																			
All cases interviewed within six months of diagnosis	-	-	-	-	-	-	*	■	*	*	*	*	*	*	*	□	*	*	□
The same interview protocol was used for cases and controls	-	-	-	-	-	-	■	■	*	■	■	■	■	■	*	□	■	■	■
The same exclusion criteria applied to both cases and controls	-	-	-	-	-	-	*	■	*	*	*	■	*	■	*	*	■	*	■
The interviewer blinded to case-control status	-	-	-	-	-	-	*	□	*	*	-	-	*	□	*	*	*	*	■
If the study used a matched case-control study design, the authors conducted a matched analysis, showed that an matched analysis was equivalent to a matched analysis and presented an unmatched analysis or adequately account for the matching factors in an unmatched analysis	-	-	-	-	-	-	-	-	-	□	-	*	-	-	-	-	-	-	-
The response rate among controls was at least 70%	-	-	-	-	-	-	*	■	■	*	-	■	*	*	*	■	*	*	■
Hospital-based controls																			
Controls were free of other forms of cancer, free of tobacco-related disease, and not have been on any special diets to treat other medical conditions (e.g., diabetes or hypertension)	-	-	-	-	-	-	-	■	■	-	*	■	-	■	■	-	■	*	-
Population-based controls																			
Controls would have been cases had they developed lung cancer	-	-	-	-	-	-	■	-	-	■	-	-	■	-	■	■	-	-	■

[a] Criteria adapted from Longnecker et al(14)

Appendix 1.

Quality criteria[a] for evaluating the design and data analysis of observation studies on total cruciferous vegetable/ITC consumption and incident lung cancer.

Table 1

Characteristics of cohort studies reporting relative risks (RR) and 95% confidence intervals (95% CI) for the association between total cruciferous vegetable consumption (highest versus lowest category) and lung cancer incidence

Reference (Study name, Year)	Country Study	Follow-up (years)	Sex	Age (at recruitment)	No. of cases	Size of cohort	Case ascertainment	Type of Dietary Questionnaire	Total cruciferous vegetables measured as cabbage, cauliflower, and Brussels sprouts plus:
(15)Chow (LBIS, 1992)	US	11.5	M	35+	219	17,633	Death certificates	FFQ	Not specified
(30)Feskanich (NHS, 2000)	US	12	F	30-55	519	121,700	Pathology	FFQ	Broccoli, cole slaw/sauerkraut
(30)Freskanich (HPFS, 2000)	US	10	M	40-75	274	51,529	Medical records	FFQ	Broccoli, cole slaw/sauerkraut
(28)Voorrips (NCS,2000)[c]	Netherlands	6	F/M	N/A	1010	3500	Pathology and cancer registries	FFQ	Kale
(29)Neuhouser (CARET, 2003)	US (Heavy smokers)	8	F/M	N/A	326	7048	Pathology and clinical records	FFQ	Broccoli, cole slaw, sauerkraut, mustard greens, turnip greens, and collards
(27)Miller (EPIC, 2004)	Europe	4	F/M	25-70	860	482,924	Histology, pathology, and cancer registries	FFQ	Broccoli

FFQ: Food frequency questionnaire; N/A: Unknown or not reported

Study's acronym: LBIS: Lutheran Brotherhood Insurance Society; NHS: Nurse's Health Study; HPFS: Health Professional Follow-up Study; NCS: Netherlands Cohort Study on Diet and Cancer; EPIC: European Prospective Investigation into Cancer and Nutrition; CARET: β-Carotene and Retinol Efficacy Trial

[a] Sex & centre stratified though author did not specified which sex

[b] RR & 95% CI of placebo arm

[c] Case cohort study (N of subcohort = 3500)

Table 2

Characteristics of case-control studies reporting odd ratios (OR) and 95% confidence intervals (95% CI) for the association between total cruciferous vegetable consumption (highest versus lowest category) and lung cancer risk, without stratification by *GST* status

Reference (Year)	Country Study	Source of Controls	Cases/ Ctrls	Sex	Age (Mean)	Case ascertainment	Type of Dietary Questionnaire	Total cruciferous vegetables measured as broccoli, cabbage, and plus:
(31)Koo (1988)	Hong Kong	Unknown (Never smokers)	88/137	F	N/A (58)	Histology	FFQ	Non-specific
(33)Pierce (1989)	Australia: Melbourne	Hospital	71/71	M	N/A (67)	Histology & cytology	Dietary questions	Brussels sprouts
(32)Agudo (1997)	Spain	Hospital	103/206	F/M	32-88 (63)	Histology	FFQ	Cauliflower
(34)Nyberg (1998)	Sweden	Hospital (Never smokers)	124/235	F/M	30-80 (N/A)	Histology & cytology	FFQ	Cauliflower
(38)Brennan (2000)	Europe: Sweden, Germany, France, Spain, UK, and Italy	Hospital (Never smokers)	506/1045	F/M	N/A	Histology	FFQ	Kale, cauliflower
(16)Spitz (2000)[b]	US	Insurance registry (Ever smokers)	503/465	F/M	N/A (61)	Histology	FFQ	Cauliflower, Brussels sprouts, kale, sauerkraut, mustard greens, turnip greens, collard greens
(35)Zhao (2001)[b]	Asia: Singapore	Hospital	233/187	F	N/A (64)	Pathology	FFQ	Cauliflower, Chinese white/ flowering cabbage, Chinese mustard, watercress, Chinese kale
(17)Seow (2001)	Asia: Singapore	Hospital	54/174	F	N/A (62)	Histology & pathology	FFQ	Total CV: Non-specific
(36)Lewis (2002)[b]	Europe and S.America	N/A (Never-smokers)	122/123	F/M	18-85 (59)	Histology	FFQ	Cauliflower
(13)Caicoya (2002)	Europe: Spain	Hospital	197/196	F/M	N/A	Pathology & cytology	FFQ	Brussels sprouts
(43)Hu (2002)	Canada	Population (Never smokers)	161/483	F	20-70+(N/R)	Histology	FFQ	
(18)Wang (2003)[b]	US	Hospital; Friends and non-blood related family members	716/939	F/M	18-85 (59)	Histology	FFQ	Coleslaw/sauerkraut, cauliflower, Brussels sprouts, kale/mustard greens
(37)Brenna n (2005)[b]	Europe: Poland, Slovakia, Czech Republic, Romania, Russia, and Hungary	Hospital & Population	2141/2168	F/M	N/A	NA	FFQ	Brussels sprouts

FFQ: Food frequency questionnaire; N/A or N/R: Unknown or not reported

[a] OR & 95% CI calculated from published data using EpiCalc 2000

[b] Bolded studies reported ORs and 95% CIs stratified by GST status

Table 3

Results of studies examining the association between total cruciferous vegetable intake and lung cancer using more than 2 categories of vegetable intake (dose-response analyses)

Reference (Year)	Types of cruciferous vegetables (CV) examined	Intake frequency	Cases/Controls[a]	OR(95% CI)	Pfor trend	Matched/Adjusted Variables			
						A	B	c	o
Cohort studies									
(15)Chow (LBIS, 1992)	Not specified	< 2 time/month	43/58,455[a]	1.0 (ref)	NR	√	*	√	√
		2-4 time/month	112/146,730[a]	0.9(0.6-1.3)					
		5-8 time/month	46/56,035[a]	1.0(0.7-1.5)					
		>8 time/month	18/25,861[a]	0.8 (0.5-1.4)					
(30)Feskanich (NHS, 2000)	Cabbage, cauliflower, and Brussels sprouts, broccoli, cole slaw/ sauerkraut	0-1.3 servings/week	NR	1.0 (ref)	NR	√	*	√	√
		1.4-2.2 servings/week		0.80 (0.62-1.05)					
		2.3-3.2 servings/week		0.85 (0.65-1.12)					
		3.3-4.8 servings/week		0.76(0.57-1.01)					
		>4.8 servings/week		0.74 (0.55-0.99)					
(30)Feskanich (HPFS, 2000)	Cabbage, cauliflower, and Brussels sprouts, broccoli, cole slaw/ sauerkraut	0-1.3 servings/week	NR	1.0 (ref)	NR	√	*	√	√
		1.4-2.1 servings/week		1.12(0.76-1.64)					
		2.2-3.3. servings/week		1.05 (0.72-1.53)					
		3.4-5.0 servings/week		0.86(0.57-1.30)					
		>5.0 servings/week		1.11(0.76-1.64)					
(28)Voorrips (NCS,2000)	Cabbage, cauliflower, and Brussels sprouts, kale	≥ 1 time/month	52/598[a]	1.0 (ref)	0.003	√	√	√	√
		2-3 time/month	150/2713[a]	0.7(0.4-1.1)					
		4 time/month	347/6676[a]	0.6 (0.4-0.9)					
		8 time/month	308/6085[a]	0.5 (0.4-0.8)					
		> 12 time/month	53/988[a]	0.5 (0.3-0.9)					
(29)Neuhouser (CARET,2003)	Cabbage, cauliflower, and Brussels sprouts, broccoli, cole slaw, sauerkraut, mustard greens, turnip greens, and collards	≥0.5 servings/week	NR	1.0 (ref)	0.01	√	√	√	√
		0.6-1.2 servings/week		1.36(0.98-1.88)					
		1.3-1.9 servings/week		0.89(0.62-1.27)					
		2.0-3.4 servings/week		0.96(0.67-1.39)					
		≥3.5 servings/week		0.68 (0.45-1.04)					

Reference (Year)	Types of cruciferous vegetables (CV) examined	Intake frequency	Cases/Controls[a]	OR(95% CI)	Pfor trend	Matched/Adjusted Variables			
						A	B	c	o
(27)Miller (EPIC, 2004)	Cabbage, cauliflower, and Brussels sprouts, and broccoli	Q1	NR	1.0 (ref)	0.25			√	√
		Q2		1.3 (0.89-1.43)					
		Q3		1.21 (0.94-1.55)					
		Q4		1.11 (0.87-1.43)					
		Q5		1.21 (0.92-1.60)					
Case-control studies									
(31)Koo (1988)	Total CV: Non-specific	Never to < 1 time/ month	88/137	1.0 (ref)	0.36	√	b	*	b
		1-3 times/month		1.3 (0.64-1.99)[b]					
		> 4 time/month		0.75 (0.28-2.00)[b]					
(33)Pierce (1989)	Total CV: Broccoli, cabbage, and Brussels sprouts	Never to 1 time/month	7/5	1.0 (ref)	0.23	b	b	b	b
		1-5 times/week	21/43	0.35(0.1-1.23)[b]					
		> 7 times/week	43/23	1.34(0.38-4.68)[b]					
(32)Agudo (1997)	Total CV: Broccoli, cabbage, and cauliflower	Low	NR	1.0 (ref)	0.13	√		√	√
		Medium	NR	0.93 (0.52-1.66)					
		High	NR	0.54(0.26-1.13)					
(34)Nyberg (1998)	Total CV: Broccoli, cabbage, and cauliflower	< Weekly	49/81	1.0 (ref)	0.33	√	√	*	√
		Once weekly	28/66	0.79 (0.42-1.52)					
		> Once weekly	47/88	1.06(0.58-1.92)					
(38)Brennan (2000)	Total CV: Broccoli, cabbage/kale, and cauliflower	Never to < Weekly	200/382	1.0 (ref)	0.76	√	√	*	√
		< Weekly to Weekly	111/234	1.0(0.7-1.3)					
		> Once weekly to Daily	113/254	1.1 (0.7-1.6)					
(17)Seow (2001)	Total CV: Non-specific	< 9 servings/week	30/59	1.0 (ref)	NR	b	b	b	b
		9-15 servings /week	13/55	0.46 (0.22-0.98)[b]					
		≥16 servings/week	11/60	0.36 (0.17-0.79)[b]					
(36)Lewis (2002)[c]	Total CV: Broccoli, cabbage, and cauliflower	< 0.9 portion/month	54/51	1.0 (ref)	0.35	√	√	*	√
		1-4 portions/month	37/53	0.58 (0.26-1.32)					
		> 4 portion/month	31/19	0.64(0.25-1.67)					

Reference (Year)	Types of cruciferous vegetables (CV) examined	Intake frequency	Cases/Controls[a]	OR(95% CI)	Pfor trend	Matched/Adjusted Variables			
						A	B	c	o
(39)Hu (2002)	Total CV: Broccoli and cabbage	≤0.9 servings/week	44/110	1.0 (ref)	0.43	√		*	√
		1-2 servings/week	50/155	0.7(0.4-1.3)					
		2.1-6.0 servings/week	32/101	0.7(0.4-1.4)					
		>6 servings/week	33/112	0.8 (0.4-1.4)					
(18)Wang (2003)[c]	Total CV: Broccoli, cabbage/coleslaw/ sauerkraut, cauliflower, Brussel sprouts, kale/ mustard greens	Low	294/329	1.0 (ref)	NR	b	b	*	b
		Medium	198/296	0.75 (0.59-0.95)[b]					
		High	224/314	0.80(0.63-1.01)[b]					
(37)Brennan (2005)[c]	Total CV: Broccoli, cabbage, and Brussel sprouts	< Once monthly	327/250	1(ref)	NR	√	√	√	√
		Once weekly	677/754	0.77 (0.62-0.95)					
		> Once weekly	1137/1164	0.78 (0.64-0.96)					

Study's acronym: LBIS: Lutheran Brotherhood Insurance Society;

NHS: Nurse's Health Study; HPFS: Health Professional Follow-up Study

EPIC: European Prospective Investigation into Cancer and Nutrition

CARET:β-Carotene and Retinol Efficacy Trial

NCS: Netherlands Cohort Study on Diet and Cancer

FFQ: Food frequency questionnaire; N/A

NR: Unknown or not reported

CV: Cruciferous vegetables

Matched/Adjusted Variables: A=Age; B=Sex; C=Smoking status/exposure; O=Other

[a] Person-years for cohort studies

[b] OR & 95% CI calculated from published data using EpiCalc 2000

[c] Bolded studies reported ORs and 95% CIs stratified by GST status

* Never smokers only; NR: Not reported

Table 4

Evidence table of case-control studies reporting odds ratios (OR) and 95% confidence limits (95% CL) for the association between total cruciferous vegetable/ITC consumption (lowest versus highest category) and lung cancer risk, stratified by GST status

Study	Cases/ Controls	Exposure	GSTM1 null		GSTT1 null		Intake Frequency	GST status	OR(95%CI)[a]	
			Cases	Ctrls	Cases	Ctrls			Present	Null
(16)Spitz,2000										
	503/465	Dietary ITC intake	246 (49.4)	226 (48.8)	132 (27.3)	104 (22.7)	≤ median > median	GSTM1	0.56 (0.38-0.82)	0.81 (0.55-1.19)
								GSTT1	0.69 (0.50-0.94)	0.53 (0.31-0.91)
								GSTM1&T1*	0.67 (0.50-0.89)	0.46 (0.20-1.04)
(35)Zhao, 2001										
	233/187	Dietary ITC intake	146 (62.7)	119 (63.6)	132 (56.7)	102 (54.5)	≤ median > median	GSTM1	0.78 (0.39-1.59)	0.55 (0.33-0.93)
								GSTT1	0.75 (0.40-1.40)	0.54(0.31-0.95)
								GSTM1/T1*	0.69(0.41-1.17)	0.47 (0.23-0.95)
(36)Lewis, 2002										
	122/123	Dietary cruciferous vegetable intake	65	53	N/A	N/A	< 1 per month	GSTM1	0.65 (0.16-2.66)	0.27 (0.06-1.33)
			(53.3)	(43.1)			> 4 per month			
(18)Wang,2003										
	716/939	Dietary cruciferous vegetables intake	404 (56.4)	516 (55.0)	138 (19.4)	185 (19.8)		GSTM1	0.61 (0.39-0.95)	1.15 (0.78-1.68)
								GSTT1	0.87 (0.63-1.21)	0.81 (0.42-1.51)
								GSTM1&T1*	0.67 (0.54-0.82)[b]	0.70 (0.39-1.26)[b]
(37)Brennan, 2005										
	2141/2168	Dietary cruciferous vegetable intake	1022	986	340	344	< once/ month	GSTM1	0.89(0.67-1.18)	0.67 (0.49-0.91)
			(47.7)	(45.4)	(15.8)	(15.8)	≥ 4 times/month			
								GSTT1	0.83 (0.66-1.03)	0.63 (0.37-1.07)
								GSTM1&T1*	0.88 (0.65-1.21)	0.28(0.11-0.67)

ITC: Isothiocyanates

PCR:Polymerase Chain Reaction

[a] Lowest (reference group) versus highest

[b] OR & 95% CI calculated from published data using EpiCalc 2000

* GSTM1&T1: GSTM1 and GSTT1; GSTM1/T1: GSTM1 or GSTT1