Proceedings of the Nutrition Society (2009), **68**, 103–110 doi:10.1017/S0029665108008884

First published online 8 December 2008

The Summer Meeting of the Nutrition Society was held at the University of Nottingham on 30 June–3 July 2008

Conference on 'Multidisciplinary approaches to nutritional problems' Symposium on 'Nutrition and health'

Cruciferous vegetable intake and the risk of human cancer: epidemiological evidence

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Proceedings of the Nutrition Society

Over several decades a number of epidemiological studies have identified the inverse associations between cruciferous vegetables and the risk of several cancers, including gastric, breast, colo-rectal, lung, prostate, bladder and endometrial cancers, via plausible physiological mechanisms. Although retrospective case–control studies have consistently reported inverse associations between the risk of these cancers and the intake of cruciferous vegetables and isothiocyanate-containing plants, current prospective cohort studies have found these associations to be weaker and less consistent. Genetic variations affecting the metabolism of glucosinolate hydrolysis products may modulate the effects of cruciferous vegetable consumption on cancer risk, which may be one of the reasons for the discrepancies between retrospective and prospective studies. In addition, methodological issues such as measurement errors of dietary exposure, misclassification, recall bias, publication bias, confounding and study design should be carefully considered in interpreting the results of case–control and cohort studies and in drawing conclusions in relation to the potential effects of cruciferous vegetables on cancers. Although recent comprehensive reviews of numerous studies have purported to show the specific protective role of cruciferous vegetables, and particularly Brassicas, against cancer risk, the current epidemiological evidence suggests that cruciferous vegetable consumption may reduce the risk only of gastric and lung cancers. However, there is at present no conclusive evidence that the consumption of cruciferous vegetables attenuates the risk of all other cancers.

Cruciferous vegetables: Cancer: Epidemiology: 3,3′-Diindolylmethane

Abundant evidence derived from descriptive and analytical epidemiological studies has indicated that higher fruit and vegetable intake is associated with a reduced risk of a variety of cancers[1–6], and several physiologically-plausible mechanisms have been suggested to explain these observations. The constituents of fruits and vegetables, including fibre, micronutrients (such as vitamins C and E and folate) and phytochemicals (such as carotenoids, phenolics, isoflavonoids, isothiocyanates (ITC) and indoles) demonstrate a range of physiological properties, including anticarcinogenic effects[7]. In particular, the phytochemicals have been reported to induce detoxification enzymes, scavenge free radicals, alleviate inflammation, inhibit malignant transformation, stimulate immune functions and regulate the growth of cancer cells[8].

In 1997 an international panel of the American Institute for Cancer Research and the World Cancer Research Fund concluded that convincing evidence existed to suggest that higher consumption of vegetables, but not fruit, protects against several cancers[3]. This conclusion was based principally on the results of case–control studies. Subsequently, however, several cohort studies have reported inconsistent results. In 2003, on the basis of all the published epidemiological evidence available, the Joint WHO/FAO Expert Consultation concluded that fruit and vegetables 'probably,' but not 'convincingly,' reduce

Abbreviations: DIM, 3,3′-diindolylmethane; GST, glutathione S-transferase; I3C, indole-3-carbinol; ITC, isothiocyanate; RR, relative risk.
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cancer risk[5]. A subsequent evaluation by the International Agency for Research on Cancer has confirmed that higher vegetable intake 'probably' lowers the risk of oesophageal and colo-rectal cancers, in addition to the conclusion that an increase in the consumption of vegetables 'possibly' reduces the risk of other cancers, including oral, pharynx, stomach, larynx, lung, ovary and kidney cancers[1].

Recently, the World Cancer Research Fund and American Institute for Cancer Research panels have issued a second report that concludes that the epidemiological findings from cohort studies conducted since the mid-1990s have rendered the overall evidence that fruits or vegetables protect against cancers somewhat less impressive. A number of studies have generated apparently conflicting results[7]. In no case now is the evidence of protection adjudged to be convincing. However, in many cases a judgment of 'probable' appears to be appropriate[4].

There may be many reasons why the protective role of vegetables against cancers remains inconclusive. Not all fruits and vegetables show the ability to suppress carcinogenesis, and there may be specific subtypes of fruits and vegetables that exhibit anticarcinogenic activity. Thus, it is crucial to determine which fruits and vegetables possess this ability. In addition, it is essential to determine which individual components present in fruit and vegetables play pivotal roles in cancer prevention. Thus, the present review has focused on the epidemiological evidence for the association between cruciferous vegetable intake and the risk of cancers. The mechanisms underlying the actions of cruciferous vegetable components are outlined and the epidemiological evidence for the effects of genetic polymorphisms on the response to cruciferous vegetable intake is discussed.

Constituents of cruciferous vegetables and mechanisms of their actions

Recently, cruciferous vegetables, rather than vegetables as a group, have drawn a great deal of attention in cancer research because of their potential protective properties. Cruciferous vegetables, including broccoli, cabbage, cauliflower, kale and mustard, are among the prevailing food crops worldwide. They are widely recognised as healthy foods, and have also been identified as rich sources of carotenoids, vitamin C, folate and soluble fibre, which may play an important role in cancer prevention[9]. In addition, the ability of cruciferous vegetables to protect against neoplastic diseases has been attributed to their high glucosinolate content[10]. Glucosinolates are converted by myrosinase in plant cells and microflora in the gastro-intestinal tract to indole-3-carbinol (I3C) and ITC[11], two phytochemicals that exhibit anticarcinogenic effects in models of animal cancer.

I3C affects the phase II enzyme systems in human subjects (for review, see Lampe[9]), inhibits carcinogenesis in animal experiments[10,11] and also inhibits the growth of a variety of human cancer cells[12,13]. When I3C is exposed to gastric acid it is converted to a number of self-condensation products, the major one of which is 3,3′-diindolylmethane (DIM)[14,15]. DIM is readily detected in the liver and faeces of rodents fed on I3C, whereas the ingested I3C is not detected in these animals[16]. These results imply that DIM, and not I3C, may mediate the observed physiological effects of dietary I3C. The results of *in vivo* animal studies have indicated that DIM shows cancer-preventive effects[17,18]. One of the suggested mechanisms by which DIM exerts its anticarcinogenic effects is the stimulation of the aryl hydrocarbon receptor. The binding of DIM to aryl hydrocarbon receptor results in the translocation of the DIM–aryl hydrocarbon receptor complex to the nucleus and subsequent binding to xenobiotic response elements in the gene promoter, thereby resulting in transactivation[19]. Aryl hydrocarbon receptor induces the transcription of the P4501A and 1B (CYP1A, CYP1B) enzyme families, glutathione S-transferase (GST) α, NAD(P)H:quinone oxidoreductase and UDP-glucuronosyltransferase[20]. In addition, DIM has been demonstrated to stimulate carcinogen detoxification[21], attenuate inflammation[22], enhance apoptosis[23,24] and arrest the cell cycle[25,26] in cancer cell lines. Research has demonstrated that caspase-8 activation contributes to the DIM-induced apoptosis of colon cancer cells[24]. In addition, it has also been demonstrated that DIM suppresses the inflammatory response to lipopolysaccharide in murine macrophages via the inhibition of NF-κB and activator protein-1 signalling[22]. Furthermore, DIM suppresses lung metastasis of 4T1 murine breast cancer cells when injected into the tail vein of syngeneic Balb/c mice (EJ Kim and JHY Park, unpublished results).

ITC formed from glucosinolates in cruciferous vegetables have been shown to effectively inhibit chemical carcinogenesis in animals. The chemopreventive effects of ITC observed in animal models is probably attributable, in part, to their ability to induce phase I activating enzymes (e.g. cytochrome P450) and phase II detoxifying enzymes (e.g. GST)[21]. ITC are reported to activate gene transcription via an antioxidant/electrophile response element[27,28]. ITC dissociate the Kelch-like-ECH-associated protein 1 from nuclear factor-erythroid 2p45-related transcription factor in the cytoplasm. The released transcription factor translocates to the nucleus where it binds to small MAF (a term derived from musculoaponeurotic-fibrosarcoma virus), thereby forming a heterodimer that binds to the antioxidant/electrophile response element, resulting in transactivation[28]. The transcription factor/MAF target genes encode for phase II detoxification or antioxidant enzymes including GSTA2, NAD(P)H:quinone oxidoreductase, haem oxygenase-1 and γ-glutamate cysteine ligase (types C and M)[20]. Via this mechanism the increased production of phase II enzymes could result in more rapid and extensive excretion of reactive molecules, whether their source is reactive oxygen species, chemical carcinogens or hormone metabolites that are substrates for GST. GST catalyse the conjugation of glutathione to ITC[29], thereby resulting in the formation of N-acetylcysteine conjugates that are later excreted by the kidney[30]. In addition, more current studies have demonstrated that ITC inhibit tumour cell proliferation both *in vitro* and *in vivo* via the inhibition of cell cycle progression and the stimulation of apoptosis via mechanisms distinct from effects on carcinogen metabolism (for review, see Zhang *et al.*[31]).

https://doi.org/10.1017/S0029665108008884 Published online by Cambridge University Press

Epidemiological studies on cruciferous vegetable intake and cancer

Epidemiological investigations have previously identified associations between diets rich in cruciferous vegetables and other glucosinolate-containing plants and a reduced risk of several cancers[7]. A recent comprehensive review[32], evaluation by the International Agency for Research on Cancer [33] and several pooled analyses[34–38] have suggested that higher intake of a specific subtype of vegetables such as cruciferous vegetables, but not vegetables as a whole, lowers the risk of a variety of cancers.

Gastric cancer

An initial review of case–control studies published up to 1996 has indicated consistent inverse associations between the intake of various vegetables and the risk of gastric cancer[39]. Eleven studies of total vegetables and eight studies of green vegetables have all reported inverse relationships. However, a panel assembled by the World Cancer Research Fund and American Institute for Cancer Research has recently concluded that vegetables ‘probably,’ but not ‘convincingly,’ reduce the risk of gastric cancer, based on a review of the results of ten large cohorts, forty-five case–control studies and nineteen ecological studies[4].

Few reports have investigated specifically the association between gastric cancer risk and cruciferous vegetable intake[40,41]. In a multi-centre hospital-based case–control study conducted in an agricultural area of Japan marginal associations were observed in the group with the highest consumption of Chinese cabbage (OR 0·61 (95% CI 0·35, 1·07)), broccoli (OR 0·60 (95% CI 0·34, 1·08)), *Hypsizigus marmoreus* (Bunashimeji) (OR 0·57 (95% CI 0·31,1·04)) and *Pholita nameko* (Nameko) (OR 0·56 (95% CI 0·30, 1·06))[40]. Another case–cohort study conducted with a sample of Hawaiian men of Japanese descent has demonstrated that the consumption of cruciferous vegetables protects against gastric cancer[41]. A significant inverse trend was noted in the age-adjusted relative risk (RR; 0·60 (95% CI 0·4, 1·0); $P = 0·03$ for trend) of gastric cancer with the intake of cruciferous vegetables.

A 2004 review by the International Agency for Research on Cancer has summarised the available results relating to gastric cancer[33]. Overall, no association (OR 0·91 (95% CI 0·67, 1·23)) with cruciferous vegetable consumption was found in cohort studies, whereas a significant inverse association was shown (OR 0·71 (95% CI 0·73, 0·90)) in case–control studies. As was the case with other cancers, the inverse relationship between cruciferous vegetable consumption and the occurrence of gastric cancer from cohort studies was less pronounced than that reported in the case–control studies.

Colo-rectal cancer

The risk of colo-rectal cancer in relation to fruit and vegetable consumption has been reported in more than fifty epidemiological studies to date[39,42]. Earlier case–control studies conducted up to 1996 have shown that inverse associations between cruciferous vegetable intake and colon cancer risk have been relatively consistent, with eight case–control studies finding inverse associations, three finding no association and only one finding a positive association[39]. The evidence from case–control studies demonstrating a protective effect of cruciferous vegetables on rectal cancer is more consistent[39]. Five case–control studies have reported inverse associations, with marked reductions in risk for high cruciferous vegetable intake *v*. low intake. In a multi-centre Japanese study inverse associations were found in the group with the highest consumption of broccoli (OR 0·18 (95% CI 0·06, 0·58)) for the risk of colo-rectal cancer[40]. These findings imply that cruciferous vegetables reduce the risk of colo-rectal cancer. However, in the Netherlands Cohort Study on Diet and Cancer[43] Brassica vegetables were shown to have inverse associations with colon cancer only in women (RR 0·51 (95% CI 0·33, 0·80); $P = 0·004$ for trend), being stronger in the distal colon than in the proximal colon. For rectal cancer positive associations for Brassica vegetables of borderline significance were demonstrated in women (RR 1·66 (95% CI 0·94, 2·94); $P = 0·05$ for trend).

In more recent studies the associations have been less consistent. In a recent review the weighted means of the RR reported for colo-rectal cancer were separately calculated for case–control and cohort studies[33]. Data were selected only for cases in which the studies provided estimates of risk for cruciferous vegetable intake together with 95% CI. In the case–control studies a significant inverse association was detected (OR 0·73 (95% CI 0·63, 0·84)), whereas in the cohort studies no overall association with cruciferous vegetables intake was detected (OR 0·96 (95% CI 0·85, 1·09)). Similarly, a pooled analysis of fourteen prospective studies has shown that associations with colon cancer risk are not significant (pooled multivariate RR 0·99 (95% CI 0·93, 1·06) for the highest tertile *v*. the lowest tertile) for cruciferous vegetables[37].

From the currently-available data it cannot be definitively concluded that the consumption of cruciferous vegetables is associated with the overall risk of colo-rectal cancer. However, inverse relationships have been demonstrated in subsites of the colo-rectum and by gender.

Lung cancer

The beneficial effect of cruciferous vegetable consumption on lung cancer risk is fairly consistent in several case–control studies that have demonstrated that higher intake of cruciferous vegetables lowers lung cancer risk[3]. A recent review estimating the weighted means of the reported RR of lung cancer has shown a significant inverse association with cruciferous vegetables from both case–control (OR 0·76 (95% CI 0·65, 0·89)) and cohort studies (OR 0·86 (95% CI 0·75, 0·98))[33]. However, several more recent cohort studies have reported conflicting results. Inverse associations between cruciferous vegetable consumption and lung cancer risk have been found in prospective studies of Finnish men[44], Dutch men and women[43] and US women[45]. In contrast, prospective studies of US men[45] and European men and women[46] have reported no such inverse association. Recently, the Pooling Project of

https://doi.org/10.1017/S0029665108008884 Published online by Cambridge University Press

Prospective Studies of Diet and Cancer[35] has evaluated the associations between specific and overall fruit and vegetable intakes and the risk of lung cancer by conducting a pooled analysis of cohort studies[35]. In this project 3206 incident lung cancer cases developed among 430 281 women and men were followed for ≤6–16 years across studies. Controlling for other lung cancer risk factors and smoking habits, a 16–23% reduction in the risk of lung cancer was detected for quintiles 2–5 of consumption for total vegetables and fruits *v*. the lowest quintile (RR 0·79 (95% CI 0·69, 0·90); $P = 0{\cdot}001$ for trend). A marginal association was detected between green leafy vegetable consumption (e.g. spinach (*Spinacia oleracea*), lettuce (*Lactuca sativa*), mustard and collard greens and kale) and lung cancer risk (pooled multivariate RR 0·93 (95% CI 0·81, 1·07) comparing intakes of ≥0·5 serving per d *v*. less than one serving per week; $P = 0{\cdot}07$ for trend; in the test for between-study heterogeneity $P = 0{\cdot}45$). However, none of the nine individual vegetables, including broccoli and cabbage, was found to be associated with the risk of lung cancer. Although the reason for discrepancies among the findings from prospective studies and between retrospective and prospective studies remains unclear, one possible explanation is that genetic variation, which affects the metabolism of glucosinolate hydrolysis products, may also influence the effects of cruciferous vegetable consumption on lung cancer risk.

Prostate cancer

Earlier epidemiological studies have suggested that a higher intake of cruciferous vegetables may lower prostate cancer risk (for review, see Verhoeven *et al*.[47]). A 2002 review has concluded that the epidemiological literature provides modest support for the premise that high cruciferous vegetable intake lowers prostate cancer risk[48]. The examples are case–control studies[49–52]. Two studies have previously reported inverse associations for cruciferous vegetables, with marked reductions in risk for high cruciferous vegetable intake *v*. low intake[49,52]. A population-based case–control study involving prostate cancer patients <65 years of age has reported that the adjusted OR for the comparison of twenty-eight or more servings of vegetables per week with fewer than fourteen servings per week is 0·65 (95% CI 0·45, 0·94; $P = 0{\cdot}01$ for trend; two-sided)[50]. For cruciferous vegetable consumption, adjusted for total vegetable intake and covariates, the OR for comparison of three or more servings per week with less than one serving per week is 0·59 (95% CI 0·39, 0·90; $P = 0{\cdot}02$ for trend). These results clearly show that high levels of consumption of vegetables, and in particular cruciferous vegetables, are associated with reduced prostate cancer risk[50]. Similarly, in a population-based case–control study that has evaluated the hypothesis that cruciferous vegetables contain potent anticarcinogenic ITC that may reduce the risk of prostate cancer, the intakes of cruciferous vegetables and broccoli, a good source of sulforaphane, were found to be associated with reduced prostate cancer risk at every level above that of the lowest consumers (adjusted 4th quartile OR 0·58 (95% CI 0·38, 0·89))[51]. This finding provides evidence suggesting that as little as two servings of cruciferous vegetables per month may reduce the risk of prostate cancer.

In contrast, associations between prostate cancer risk and cruciferous vegetable intake derived from prospective studies have been less consistent, with some showing inverse associations[53,54] and others finding no significant association[55]. In a recent prospective study of the screening arm of the Prostate, Lung, Colo-rectal, and Ovarian Cancer Screening Trial vegetable consumption was not found to be associated with overall prostate cancer risk[54]. However, the risk of extraprostatic prostate cancer (stage III or IV tumours) was shown to be reduced with increasing vegetable intake (RR 0·41 (95% CI 0·22, 0·74) for high intake *v*. low intake; $P = 0{\cdot}01$ for trend). This association was explained principally by the intake of cruciferous vegetables (RR 0·60 (95% CI 0·36, 0·98) for high *v*. low intake; $P = 0{\cdot}02$ for trend), particularly, broccoli (RR 0·55 (95% CI 0·34, 0·89) for more than one serving per week *v*. less than one serving per month; $P = 0{\cdot}02$ for trend) and cauliflower (RR 0·48 (95% CI 0·25, 0·89) for more than one serving per week *v*. less than one serving per month; $P = 0{\cdot}03$ for trend). These results suggest that high intake of cruciferous vegetables, including broccoli and cauliflower, may be associated with a reduced risk of advanced prostate cancer, and in particular metastatic prostate cancer.

Multiple dietary evaluations of 2969 cases of prostate cancer from 1986 to 2000 have indicated no overall relationship between the baseline intake of cruciferous vegetables and prostate cancer risk[53]. However, an inverse relationship between prostate cancer risk and cruciferous vegetable intake was found among men <65 years of age. Furthermore, when analysis was restricted to men who had undergone a prostate-specific antigen test and who had prostate gland-confined cancer the inverse relationship was shown to be stronger. The differential findings underlie the importance of control for screening, age of patients and stage of cancer (organ-confined or metastatic).

Breast cancer

Substantial epidemiological evidence of an inverse association between consumption of cruciferous vegetables and the risk of breast cancer has been derived from available case–control studies (overall OR 0·87 (95% CI 0·78, 0·96))[33]. Additionally, other reports have suggested that the consumption of certain cruciferous vegetables may attenuate the risk. In the Western New York Diet Study, a case–control study of Caucasian women with incident breast cancer, a marginal inverse association has been shown between the consumption of cruciferous vegetables, particularly broccoli, and breast cancer risk in premenopausal women (4th quartile OR 0·6 (95% CI 0·40, 1·01); $P = 0{\cdot}058$), with weaker or non-existent associations among post-menopausal women[56]. These data indicate that cruciferous vegetables may have a role in reducing the risk of premenopausal breast cancer. The association has also been assessed in a case–control study conducted in Sweden, a country with a wide range of cruciferous vegetable intake[57]. Brassica vegetable intake was found to be inversely associated with breast cancer risk (multivariate

OR 0·76 (95 % CI 0·62, 0·93) for highest quartile of intake *v*. lowest quartile; $P=0{\cdot}01$ for trend). Further detailed analysis of the data shows that the OR among women in the highest decile (10 %) of cruciferous vegetable consumption (median, 1·5 servings per d) *v*. the lowest decile (virtually no consumption) is 0·58 (95 % CI 0·42, 0·79; $P=0{\cdot}003$).

However, currently-available cohort studies have detected no association between cruciferous vegetable intake and breast cancer risk[33]. A pooled analysis of eight cohort studies has reported no associations between the intakes of individual or overall fruit and vegetables and breast cancer risk[34]. In this study 7377 incident invasive breast-cancer cases occurring among 351 825 women were followed for 6–16 years. Total fruit and vegetables were found to be marginally associated with the risk of breast cancer (pooled multivariate RR 0·93 (95 % CI 0·86, 1·00); $P=0{\cdot}12$ for trend) in comparisons of the highest intake quartile *v*. lowest intake quartile. However, the intake of cruciferous vegetables (broccoli, Brussels sprouts and cabbage) was not found to be significantly associated with breast cancer risk.

In summary, although several case–control and cohort studies have reported inverse relationships in a variety of populations, there is no conclusive epidemiological evidence to suggest that cruciferous vegetables have a causative function in reducing breast cancer risk.

Bladder cancer

To date, two prospective[58,59] and one retrospective[60] epidemiological studies have assessed the specific role of cruciferous vegetables or dietary ITC against bladder cancer. The Health Professionals Follow-up Study[58] has reported a weak non-significant inverse association between total fruit and vegetable intake and the risk of bladder cancer. However, a significant inverse association was found for cruciferous vegetables (RR 0·49 (95 % CI 0·32, 0·75) for the highest category of cruciferous vegetable intake *v*. the lowest category). Among individual cruciferous vegetables broccoli (RR 0·61 (95 % CI 0·42, 0·87)) and cabbage (RR 0·57 (95 % CI 0·33, 0·97)) were found to be significantly associated with bladder cancer risk. These observations show that high cruciferous vegetable consumption may reduce bladder cancer risk, but other vegetables and fruits may not exert marked beneficial effects against this cancer.

In the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study 27 111 male cigarette smokers aged 50–69 years were followed over a median of 11 years, during which 344 of the men developed bladder cancer[59]. However, no associations between the consumption of cruciferous vegetables and bladder cancer risk were observed in this prospective cohort. These findings indicate that cruciferous vegetable intake is not likely to be associated with bladder cancer risk in smokers, but these results may not be generalisable to non-smokers.

In a recent case–control study involving 697 newly-diagnosed bladder cancer cases and 708 healthy controls matched by age, gender and ethnicity it has been shown that ITC from cruciferous vegetable consumption protect against bladder cancer[60]. ITC intake was found to be associated inversely with bladder cancer risk (OR 0·71 (95 % CI 0·57, 0·89)). This protective effect was found to be stronger in older individuals (64 years old), men, ever smokers and heavy smokers in stratified analysis.

Endometrial cancer

A recent systematic review of literature and meta-analysis[61] has summarised the current evidence for a relationship between fruit and vegetable intake and endometrial cancer by utilising data from pertinent cohort and case–control studies published up to June 2006[62–64]. The summary OR for the highest category of intake *v*. the lowest category were 0·71 (95 % CI 0·55, 0·91) for total vegetables and 0·85 (95 % CI 0·74, 0·97) for cruciferous vegetables. Summary OR for increasing intake levels at 100 g/d were 0·90 (95 % CI 0·86, 0·95) for total vegetables and 0·79 (95 % CI 0·69, 0·90) for cruciferous vegetables. Currently-available results, derived exclusively from case–control studies, appear to suggest that high consumption of vegetables, specifically cruciferous vegetables, may moderately reduce endometrial cancer risk. To date, no cohort study has been conducted to evaluate the relationship between endometrial cancer and individual fruit and vegetables. Additional prospective data from well-conducted population-based studies will be necessary before a firm conclusion can be drawn.

Genetic polymorphisms and response to cruciferous vegetable intake for cancer risk

Although a comprehensive review of epidemiological evidence relating to the protective role of cruciferous vegetables and/or ITC against cancers suggests a putative protective role, as discussed earlier, it remains an open question as to whether consumption of cruciferous vegetables and/or ITC may reduce the risk. One possible explanation for the inconsistent evidence across epidemiological studies may be variations in genes that are directly and indirectly involved in carcinogenesis in relation to cancer risk. Genetic polymorphisms associated with the exposure to environmental risk factors for cancer can affect the cancer susceptibility of each individual, when coupled with the relevant carcinogen exposures. It has recently been shown that genetic polymorphisms of phase I and phase II enzymes, which are components of the biotransformation pathways, alter an individual's response to cancer chemopreventive foods, including cruciferous vegetables[65,66]. ITC from cruciferous vegetables both induce and are substrates for the GST, a family of phase II enzymes involved in the detoxification of carcinogens, environmental toxins and oxidative stress products, by catalysing conjugation with glutathione[67]. Several genetic polymorphisms (*GSTM1, GSTM3, GSTT1, GSTP1, GSTA1*) of GST that exert an effect on GST enzyme activity have been assessed in relation to human cancers[67,68]. It is reported that the enzyme activities are reduced or completely absent in individuals with null genotypes of *GSTM1* and/or *GSTT1*[66]. Lower and/or absent GST activity in

https://doi.org/10.1017/S0029665108008884 Published online by Cambridge University Press

such individuals could result in slower elimination of and more extended exposure to ITC following the ingestion of cruciferous vegetables.

Numerous epidemiological studies have assessed whether inverse associations between ITC intake from cruciferous vegetables and cancer risk are altered in individuals with GST gene polymorphisms in relation to colo-rectal[69], lung[70,71], breast[56,67,72], head and neck[73], kidney[74] and bladder cancer[60] and colo-rectal adenoma[75,76]. Overall, associations between ITC intake and the risk of lung, kidney and colo-rectal cancer are modified by the *GSTM1* and/or *GSTT1* genotypes.

A meta-analysis using results from 130 genetic association studies of five *GST* variants (*GSTM1*-null, *GSTT1*-null, I105V, and A114V polymorphisms in the *GSTP1* gene, and *GSTM3* intron 6 polymorphism) and lung cancer risk published before 2005 (a total of 30 397 controls and 23 452 lung cancer cases), has reported RR for lung cancer of 1·18 (95% CI 1·14, 1·23) and 1·09 (95% CI 1·02, 1·16) for the *GSTM1*-null and *GSTT1*-null polymorphisms respectively[68]. However, no significant associations were found when analysis was restricted to the larger studies with ≥ 500 cases (RR 1·04 (95% CI 0·95, 1·14) for *GSTM1* and 0·99 (95% CI 0·86, 1·11) for *GSTT1*).

Higher consumption of ITC or a higher level of urinary ITC have been found to be inversely related to lung cancer risk, particularly among *GSTM1*-null and/or *GSTT1*-null individuals in a nested case–control study within a prospective cohort of Chinese men and women (Shanghai, China)[70,71] and a hospital-based case–control study of Singaporean Chinese women[77]. Among those with *GSTM1*- and/or *GSTT1*-null genotypes the risk of lung cancer associated with ITC level was predominant.

Increased renal cell carcinoma risk has been observed for *GSTT1*-null or both *GSTM1/T1*-null carriers compared with *GSTM1*-present and *GSTT1*-present carriers among individuals with a low intake of cruciferous vegetables in the Central and Eastern European Kidney Cancer Study[74].

A prospective study of 63 257 middle-aged women and men in the Singapore Chinese Health Study has shown a 57% reduction in colo-rectal cancer risk in high-ITC consumers *v.* low-ITC consumers (OR 0·31 (95% CI 0·12, 0·84)) among subjects with both *GSTM1*- and *GSTT1*-null genotypes[69]. Furthermore, inverse relationships between broccoli consumption and the risk of colo-rectal adenomas have been found in subsets of GST genotypes (*GSTM1*-null and *GSTM1/T1*-null genotypes).

The Western New York Diet Study has reported a marginal reduction in breast cancer risk with high cruciferous vegetable intake only in premenopausal women (OR 0·60 (95% CI 0·40, 1·01); $P = 0{\cdot}058$)[56]. Modification of the association by *GSTM1* and/or *GSTT1* genotypes was not found to be significant for either the post- or premenopausal group. More recently, possible associations between *GSTA1* polymorphisms and breast cancer risk in relation to cruciferous vegetable consumption has been evaluated in the Long Island Breast Cancer Study Project[67], a population-based case–control study (1089 controls and 1036 cases)[78]. Although breast cancer risk was not affected by these genotypes among women who consumed smaller amounts of cruciferous vegetables, the risk was found to be elevated significantly in those with the *GSTA1* *B/*B genotypes as compared with those with the common *A/*A genotypes.

Concluding remarks

Over several decades, a number of epidemiological studies have identified associations between dietary components such as vegetables and fruits and reduced risk of several cancers. More specifically, a variety of vegetables and fruits have been individually assessed in order to identify the most effective cancer-preventing components. Although relatively-few retrospective and prospective studies have evaluated the associations between cruciferous vegetables and other glucosinolate-containing plants and the risk of cancers, the results indicate that higher intake of specific types of vegetables such as cruciferous vegetables, but not vegetables as a whole, may lower the risk of several cancers[34–38].

Several methodological issues such as measurement errors of dietary exposure, misclassification, recall bias, publication bias, confounding and study design should be carefully considered in interpreting the findings from the case–control and cohort studies, and in reaching a conclusion about the potential effects of cruciferous vegetables on cancers.

Although recent comprehensive reviews of numerous studies purport to show a specific protective effect of cruciferous vegetables, particularly Brassicas, on cancer risk, the currently-available epidemiological evidence suggests that cruciferous vegetable consumption may reduce the risk of gastric and lung cancers. However, it would still be premature to conclude that the consumption of cruciferous vegetables reduces the risk for all other cancers.

Acknowledgements

This study was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD; KRF-2006–311-C00176) and by the KOSEF (Korea Science and Engineering Foundation) under grant no. R01–2006–000–10621–0. The authors declare no conflict of interest.

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https://doi.org/10.1017/S0029665108008884 Published online by Cambridge University Press