

Dietary Intake of Isothiocyanates: Evidence of a Joint Effect with Glutathione *S*-Transferase Polymorphisms in Lung Cancer Risk¹

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Abstract

Isothiocyanates (ITCs) are nonnutrient compounds in cruciferous vegetables with anticarcinogenic properties. One proposed mechanism for their protective action is through down-regulation of cytochrome P-450 biotransformation enzyme levels and induction of phase II detoxifying enzymes. Because ITCs also serve as a substrate for *GSTs*, we evaluated dietary intake of ITCs and *GSTM1* and *GSTT1* genotype information in a lung cancer case-control study. There were 503 newly diagnosed lung cancer cases (264 men and 239 women) identified from The University of Texas M. D. Anderson Cancer Center and 465 controls (252 men and 213 women) recruited from enrollees in a local managed care organization. Subjects had an in-person interview including a semiquantitative food frequency questionnaire, and blood samples were obtained for genotyping. Cases reported significantly lower ITC intake per day compared with controls ($P = 0.009$). There was no main effect associated with the *GSTM1* null genotype [odds ratio (OR) = 1.09]. However, there was a statistically significant OR of 1.41 associated with the *GSTT1* null genotype. On stratified analysis, low ITC intake and the *GSTM1* null genotype were associated with increased lung cancer risk in current smokers, with an OR of 2.22 [confidence interval (CI) = 1.20–4.10]. For current smokers with the *GSTT1* null genotype, the OR with low ITC intake was 3.19 (CI = 1.54–6.62). The comparable OR in the presence of both null genotypes was 5.45 (CI = 1.72–17.22). These effects were not demonstrable for former smokers by *GSTM1* genotype, although the risk for low ITC intake and *GSTT1* null genotype was 1.79 (CI = 0.95–3.37). Thus, current

smokers who are homozygous null for the *GST* null genotype and who consume less carcinogenic blocking compounds are at higher lung cancer risk. Some of the inconsistencies reported in the role of *GST* genotypes in lung cancer risk could be due to unexpected confounding from dietary factors.

Introduction

ITCs³ are nonnutrient compounds in cruciferous vegetables, predominantly of the *Brassica* genus. They occur as glucosinolates, and they undergo enzymatic cleavage to ITCs and indoles on chopping or chewing of the vegetables (1). ITCs are effective inhibitors of tumorigenesis in animal model systems (2, 3). One proposed mechanism for their protective action is through down-regulation of cytochrome P-450 biotransformation enzyme levels and direct inhibition of their catalytic activities, together with induction of phase II enzymes that detoxify any residual electrophilic metabolites from the phase I enzymic activity (4, 5). Different ITCs exert different effects and may exhibit either one or both of these activities.

Well-designed cohort and case-control studies have demonstrated the protective effect of dietary cruciferous vegetables in humans, specifically against lung cancer (6). Hecht *et al.* (7) have shown that consumption of average portions of vegetables can result in the release of tens of milligrams of ITCs. For example, consumption of 2 ounces of watercress results in the release of about 12 mg of PEITC and, in a group of smokers, inhibited the oxidative metabolism of NNK (7).

Epidemiological studies examining the protective association of cruciferous vegetables within smoking strata have had mixed results. Gao *et al.* (8) found the protective effect to be most apparent in current smokers (OR = 0.3). However, Steinmetz *et al.* (9) reported an effect only among ex-smokers (OR = 0.4). Koo (10) noted no association with lung cancer risk in women who had never smoked. Few studies have evaluated the effect of these dietary constituents together with adverse metabolic genotypes. Because ITCs induce *GSTs* and serve as a substrate for *GSTs*, we therefore evaluated dietary intake of ITCs in a lung cancer case-control study and integrated these data with *GSTM1* and *GSTT1* genotype information and smoking status to assess their joint effects.

Materials and Methods

The cases and controls were accrued from a molecular epidemiological study of susceptibility markers for lung cancer described previously (11, 12). This study recruited newly diagnosed lung cancer patients before treatment from The

Received 3/29/00; revised 7/21/00; accepted 8/8/00.

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¹ Supported by National Cancer Institute Grants CA 55769 (to M. R. S.) and CA 68437 (to W. K. H.).

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³ The abbreviations used are: ITC, isothiocyanate; PEITC, phenethyl ITC; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; OR, odds ratio; CI, confidence interval.

University of Texas M. D. Anderson Cancer Center. There were no age, histological, or stage restrictions, but all cases were histologically confirmed. Control subjects were recruited from a large multispecialty managed care organization in the Houston metropolitan area and were matched to the cases by age (± 5 years), ethnicity, sex, and smoking status (never, former, or current). Because of the small numbers of minority subjects recruited, we report here only the data for white participants.

After informed consent was obtained, a structured interview of approximately 45 min was conducted, and a blood sample was drawn. Dietary data were obtained by a modified version of the dietary segment of the National Cancer Institute Health Habits and History Questionnaire (13). This questionnaire includes a semiquantitative food frequency list, an open-ended food section, and select food preparation questions. The validity and reliability of this questionnaire are well documented (14). The modified questionnaire lists 135 food and beverage items and includes ethnic foods commonly consumed in the Houston area. Interviewers asked about the dietary intake of control subjects during the previous year and the dietary intake of cases in the year before diagnosis.

Demographic and nutritional data were merged with laboratory data. Ever-smokers were defined as individuals who had smoked more than 100 cigarettes in their lifetime. Pack-years were calculated using the average number of cigarette packs smoked per day and the number of years smoked. Former smokers were defined as ever-smokers who had quit at least 1 year before the date of the interview. The dietary data were analyzed with DietSys (version 4.01), the nutrient analysis program designed to accompany the National Cancer Institute Health Habits and History Questionnaire (15). We added ITC values for broccoli, cauliflower, and cabbage (16), and we computed intake of ITCs in milligrams per 1000 kilocalories and weekly intake of vegetables containing ITCs in 0.5-cup servings. These data were dichotomized at the median value of the controls. Pearson's χ^2 test was used to examine differences in distributions of genotype between cases and controls. The association between the genotypes and lung cancer risk was further examined by use of unconditional and conditional logistic regression analysis to calculate the OR and 95% CIs. Because results for both were similar, we report only the data from the unconditional analysis. Joint effects of the *GST* genotypes with ITC intake were estimated using the *a priori* low-risk genotype and higher ITC intake as a common referent group. Tests for interaction were based on the *P* (two-sided) of the likelihood ratio test for adding the interaction term (genotype by ITC intake) to the model that included the main effect variable (genotype). After DNA extraction, the presence or absence of the *GSTM1* and *GSTT1* loci was determined by using standard PCR techniques (17, 18).

Results

There were 503 lung cancer cases (264 men and 239 women) and 465 controls (252 men and 213 women; Table 1). Their mean ages were 62.3 and 60.9 years, respectively. Because case enrollment precedes control selection, perfect matching has not yet been achieved. There were more current smokers among the cases (43.9%) than the controls (36.2%; *P* = 0.03), and the cases were heavier smokers (mean pack-years, 51.0 versus 45.1; *P* = 0.003).

The mean total ITC intakes were 0.47 ± 0.51 mg/1000 kcal for the cases and 0.58 ± 0.84 mg/1000 kcal for the controls (*P* = 0.009; Table 1). The average number of 0.5-cup servings

Table 1 Distribution of selected characteristics of lung cancer cases and controls

	Cases (n = 503)	Controls (n = 465)	<i>P</i>
Sex (%)			
Male	264 (52.5)	252 (54.2)	0.595
Female	239 (47.5)	213 (45.8)	
Age, yrs (SD)	62.3 (9.43)	60.9 (10.10)	0.049
Smoking status (%)			
Never	46 (9.3)	39 (8.4)	0.027
Former	230 (46.7)	257 (55.4)	
Current	216 (43.9)	168 (36.2)	
Pack-years (SD)	51.0 (35.05)	45.1 (32.12)	0.003
Cigarettes/day (SD)	27.1 (15.94)	26.9 (16.00)	0.510
<i>GSTT1</i> null (%)	132 (27.3)	104 (22.7)	0.106
<i>GSTM1</i> null (%)	246 (49.4)	226 (48.8)	0.856
Calories/day (SD)	2030.9 (698.44)	2009.7 (667.65)	0.679
Total ITC ^a day (SD)	0.47 (0.51)	0.58 (0.84)	0.009
Servings ^b week (SD)			
Broccoli	0.84 (0.98)	1.13 (1.80)	0.007
Cauliflower, Brussels sprouts	0.31 (0.53)	0.45 (1.42)	0.001
Coleslaw, cabbage, sauerkraut	0.58 (0.85)	0.63 (0.93)	0.479
Mustard greens, turnip greens, collard greens, kale	0.38 (0.71)	0.33 (0.70)	0.123
Total cruciferous vegetables	2.11 (1.85)	2.54 (3.36)	0.080

^a Dietary intake in mg/1000 kcal.

^b Serving = 0.5 cup of vegetables.

of broccoli per week was 0.84 for the cases and 1.13 for the controls (*P* = 0.007). For cauliflower and Brussels sprouts (which were reported together), the comparable values were 0.31 and 0.45, respectively (*P* = 0.001). The overall number of servings per week for the cruciferous vegetables was 2.11 for the cases and 2.54 for the controls (*P* = 0.08).

Women had statistically significantly higher ITC intake than men, both among the controls (*P* = 0.001) and the cases (*P* = 0.008; data not shown). Among the cases, current smokers reported the lowest ITC intake: 0.35 ± 0.36 versus 0.56 ± 0.59 mg/1000 kcal (*P* < 0.001) for former smokers and 0.50 ± 0.56 versus 0.67 ± 1.02 mg/1000 kcal (*P* = 0.009), respectively, for the comparable controls (data not shown). The adjusted risk estimates for lower intake of ITC was OR = 1.72 (CI = 1.13–2.62) in current smokers and OR = 1.30 (CI = 0.90–1.88; data not shown) in former smokers.

The *GSTM1* genotype was homozygous null in 49.4% of the cases and 48.8% of the controls. The comparable prevalences of the homozygous *GSTT1* null genotype were 27.3% and 22.7%, respectively (*P* = 0.106). Both null genotypes were present in 13.0% of the cases and in 10.0% of the controls. None of these differences were statistically significant. There was no evidence of a main effect for the *GSTM1* null genotype. The overall OR, adjusted for age, gender, smoking status, and ITC intake, was 1.09 (CI = 0.84–1.41). However, the risk associated with the *GSTT1* null genotype was OR = 1.41 (CI = 1.03–1.93; data not shown). For current smokers specifically, the comparable risk estimates were OR = 1.34 (CI = 0.88–2.04) for *GSTM1* and OR = 1.50 (CI = 0.89–2.53) for *GSTT1*.

We next performed stratified analysis separately by smoking status, using as the referent group individuals whose ITC intake was above the median value in the controls and who had the non-null genotype (Table 2). There were too few never-smokers to analyze similarly. Among current smokers, for low ITC intake and the *GSTM1* null genotype, the OR was 2.22 (CI = 1.20–4.10). For current smokers with the *GSTT1* null genotype, the OR for the joint effect with low ITC intake was

Table 2 Stratified analyses by genotype and dietary intake of ITC in lung cancer

Dietary intake ^a	Genotype	Current smokers			Former smokers		
		Case	Control	OR (95% CI) ^b	Case	Control	OR (95% CI) ^b
<i>GSTM1</i>							
High	Positive	28	39	1.0	53	70	1.0
Low	Positive	77	51	2.11 (1.15–3.85)	69	59	1.59 (0.96–2.64)
High	Null	38	34	1.55 (0.79–3.04)	59	69	1.14 (0.69–1.90)
Low	Null	71	44	2.22 (1.20–4.10)	46	57	1.14 (0.66–1.96)
<i>GSTT1</i>							
High	Positive	43	54	1.0	80	102	1.0
Low	Positive	106	78	1.71 (1.04–2.82)	84	88	1.29 (0.84–2.00)
High	Null	18	17	1.31 (0.60–2.85)	29	38	1.06 (0.59–1.89)
Low	Null	37	15	3.19 (1.54–6.62)	31	27	1.79 (0.95–3.37)
Both							
High	Positive	54	63	1.0	96	122	1.0
Low	Positive	129	89	1.68 (1.07–2.65)	104	103	1.35 (0.91–2.00)
High	Null	8	8	1.09 (0.38–3.14)	15	18	1.08 (0.51–2.30)
Low	Null	18	4	5.45 (1.72–17.22)	13	12	1.71 (0.72–4.08)

^a Values are in mg/1000 kcal, dichotomized at median value in controls (≤ 0.39 mg).

^b Adjusted by age and sex.

3.19 (CI = 1.54–6.62). A similar, but larger, joint effect was evident for both null genotypes combined. The adjusted OR was 5.45 (CI = 1.72–17.22). These effects were not demonstrable for former smokers by *GSTM1* genotype (Table 2). However, in the stratum with low ITC and null *GSTT1* genotype, the OR was 1.79 (CI = 0.95–3.37). In a multiplicative interaction model, none of the interaction terms were statistically significant (data not shown).

Discussion

Individuals homozygous for the *GSTM1* and *GSTT1* null alleles are common (20–50%) in most populations, but the associated cancer risks appear to be small. A recent meta-analysis of 19 case-control studies reported an overall lung cancer risk of only 1.14 (CI = 1.04–1.25) associated with the *GSTM1* null genotype (19). In this analysis, there was no overall case-control difference in distribution of the *GSTM1* null genotype, and there was a main effect that did not deviate much from 1. However, there was a statistically significant OR of 1.41 for the *GSTT1* null genotype. In addition, the main effect was notably larger for dietary ITC intake (OR = 1.72).

In the stratified analysis for joint effects in current smokers, the relative risk for the *GSTM1* null genotype in the presence of low ITC intake was 1.05 (2.22:2.11). The comparable risk estimate for the *GSTT1* null genotype was 1.87 (3.19:1.71). Of interest, the risk for both null genotypes in association with low ITC intake was 3.24 (5.45:1.68).

ITCs are potent inhibitors of NNK metabolism (20) both *in vivo* and *in vitro* (21). PEITCs and benzyl ITCs inhibit NNK-induced and benzo(a)pyrene-induced lung tumorigenesis, respectively. A recent study concluded that PEITC specifically exerts its preventive effects only when given concomitantly with the carcinogen (22). This parallels our own findings of a protective effect only in current smokers.

Bioavailability of ITCs at the target tissue level depends in part on their metabolic clearance *in vivo*. The major metabolic route is through mercapturic acid formation, a pathway that requires participation of the *GST* family of enzymes (23). Seow *et al.* (16) showed a higher urinary excretion of ITCs in *GSTT1*-positive versus -null study subjects. This effect was most pronounced for subjects in the highest tertile of cruciferous veg-

etable intake. The null genotype was associated with lower excretion levels.

Lin *et al.* (24) have published data showing a protective effect for subjects with high dietary broccoli intake and who were null for *GSTM1* with a lower colon adenoma prevalence, an unexpected effect for the null *GST* phenotype. Broccoli contains the ITC, sulforaphane, that is itself a substrate for *GSTM1*, thereby reducing the levels of ITC available for Phase I inhibition and induction of Phase II detoxification. Thus in the *GSTM1* null subject, sulforaphane tends to be conserved (23). Lin *et al.* hypothesized that these subjects had high intake and slower conjugation and excretion of ITCs (24). There was no interaction with smoking (24). We reanalyzed our data on broccoli intake in 0.5-cup servings to be comparable with their data. Among current smokers, there was a statistically significant protective effect of higher broccoli intake in association with the non-null *GSTM1* genotype (OR = 0.50; CI = 0.27–0.90). However, for individuals with the null genotype, the protective effect was attenuated (OR = 0.75; CI = 0.40–1.39). We found a similar pattern for the *GSTT1* genotypes with ORs of 0.68 (CI = 0.41–1.11) and 0.78 (CI = 0.37–1.62), respectively. Conversely, in current smokers with lower broccoli intake, the risk associated with the null *GSTT1* genotype was 2.00 (CI = 1.01–3.98).

There could be several explanations for the disparity in our results compared with those of Lin *et al.* (24). The effect of ITC intake may differ among different cancer sites. The *GSTM1* null genotype has not been associated with increased risk of colorectal adenomas in smokers (25). On the other hand, modest but fairly consistent associations have been noted in lung cancer in association with the null genotype. Another consideration is the bioavailability of ITC at the target tissue level. *GSTM1* is expressed in the liver and small intestine but is less expressed in the large intestine (26) and is virtually absent in lung tissue. Nevertheless, benzo(a)pyrene diol epoxide adducts are found in tissues that do not themselves activate benzo(a)pyrene (27, 28), because once in the circulation, benzo(a)pyrene diol epoxide is protected by binding to serum albumin and lipoproteins and reaches all parts of the body.

In the United States, mean intake frequency of cruciferous vegetables is twice per week (29). Our cases and controls

consumed an average of 2.11 and 2.54 half (0.5)-cup servings per week, respectively. In the study of Lin *et al.* (24), mean intake was 2.9 half (0.5)-cup servings per week for their cases and 3.5 half (0.5)-cup servings for the controls. The lower intake of cruciferous vegetables in our controls could be because the majority of our controls were current or former smokers, and almost one-half (43%) of their controls were never-smokers. In many populations, smokers tend to eat fewer vegetables. The mean numbers of 0.5-cup servings of broccoli per week for their cases and controls were also higher than ours (1.2 versus 1.5 half (0.5)-cup servings for their cases and controls, respectively, compared with 0.84 and 1.13 half (0.5)-cup servings for cases and controls in our data). The cut point we used (0.39 mg ITCs/1000 kcal/day) can be obtained by consuming the equivalent of approximately 0.5 cup of broccoli per week, 2 cups of cauliflower per week, or 1 cup of cabbage per week, assuming an average caloric intake of 2000 kcal/day.

In addition to glucosinolates, these vegetables also contain many other compounds that are postulated to have protective effects, including carotenoids, vitamin C, folic acid, fiber, and protease inhibitors. It is plausible that individuals likely to be at increased risk for lung cancer (current smokers who are homozygous null for protective genotypes) who also consume the least amount of carcinogenic blocking compounds would find themselves in the highest risk category.

There are inherent limitations in our study, including use of food frequency data to estimate ITC intake, possible recall bias, and a sample size not large enough for testing interactions for statistical significance. Dietary ITCs have rarely been considered as confounding factors in molecular epidemiology studies. The strength of the effect observed in this study suggests that ITCs may have more impact on lung cancer risk in current smokers than metabolizing genes. This is especially noteworthy because the genes are measured with minimal error, whereas dietary assessment is associated with substantial measurement error. Some of the inconsistencies that have been noted in the study of the effect of *GST* genotypes could be due to unexpected confounding factors in the diet. These data highlight the complexity and challenges inherent in the analysis of diet-gene interactions.

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Cancer Epidemiol Biomarkers Prev 2000;9:1017-1020.

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