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Dietary Isothiocyanates, Glutathione S-Transferase M1 (*GSTM1*), and Lung Cancer Risk in African Americans and Caucasians from Los Angeles County, California

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Abstract

Isothiocyanates, found in cruciferous vegetables, are anti-carcinogenic. Racial differences in smoking do not fully account for the African American excess lung cancer incidence. African Americans consume more cruciferous vegetables than US Whites. Impact on lung cancer risk is unknown. Glutathione S transferase M1 (*GSTM1*) gene promotes urinary isothiocyanate excretion. We evaluated dietary isothiocyanates and lung cancer using a population-based case-control study of 933 African Americans and Caucasians (non-Hispanic US White) from Los Angeles County, California (311 cases; 622 controls). Broccoli, cauliflower, greens and cabbage food-frequency variables represented isothiocyanates. Isothiocyanates were protective for lung cancer risk. Adjusted odds ratio (OR) for the uppermost quartile, > 80 μMol isothiocyanates/week, compared to lowest, was 0.65 (95% confidence interval (CL) = 0.41 – 1.00, trend p = 0.02). Association was stronger among subjects with homozygous deletion of *GSTM1* (OR=0.52; 95% CL = 0.31 – 0.86), than subjects with at least one *GSTM1* copy (OR = 0.77; 95% CL = 0.49 – 1.21). Difference was not statistically significant (p = 0.16). Despite African Americans consuming more cruciferous vegetables, the isothiocyanate association did not vary by race (p=0.52). Reduced lung cancer risk with higher isothiocyanate intake may be slightly stronger among subjects with deletion of GSTM1.

Keywords

lung neoplasms; isothiocyanates; *Brassica*; *GSTM1*; African Americans

INTRODUCTION

There is controversy about whether vegetable intake reduces lung cancer risk. Although early observational studies suggested that elevated vegetable intake reduces the risk of lung cancer (1–8), evidence from recent large pooled studies and prospective cohorts has been inconclusive (9–13).

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Cruciferous vegetables contain a variety of biologically active constituents that may play a role in cancer protection (14). Among these, isothiocyanates are a class of compounds with anticarcinogenic properties. Experimental studies in animals show that isothiocyanates hinder lung carcinogenesis mainly through inhibition of tobacco smoke procarcinogen activation by phase 1 enzymes (cytochrome P450s), and enhancement of detoxification by phase 2 enzymes (glutathione S-transferases) (GST) (15). In addition, the ability of isothiocyanates to inhibit cell proliferation and induce apoptosis has recently been shown to contribute to protection against lung carcinogenesis (16).

Several years ago we reported that a urinary biomarker of isothiocyanate intake was inversely related to lung cancer risk in a population (Shanghai) that consumes high levels of cruciferous vegetables, and that this protective effect was greatest in subjects genetically deficient in glutathione-S-transferase M-1 (*GSTM1*) and T1 (*GSTT1*) (17). This observation has been confirmed, using dietary questionnaire data in a US Texas population (18), in Singapore Chinese (19), in a European population from Central and Eastern Europe (20), and, among non-smokers from Europe and South America (21), although one US study and one Danish study found opposite effects with the strongest protection found among *GSTM1* intact subjects who had high intakes of cruciferous vegetables (22, 23).

No study has yet evaluated dietary isothiocyanate consumption among a multi-racial population that included African-Americans. African-Americans are of interest in this regard because of their reported higher consumption of cruciferous vegetables. Greens, a dish typically made from mustard or collard greens, which is rarely consumed among US Whites outside of the South, is a common food item in typical African American diets (24).

African Americans exhibit a higher incidence of lung cancer than other American ethnic groups (25). Patterns of excess lung cancer risk among African-American men may be due to a higher prevalence of current smoking. However African-American smokers consume fewer cigarettes per day than White men (26), suggesting that the elevated incidence cannot be fully attributed to smoking differences. Explanations for racial differences in lung cancer incidence most likely involve variation in other environmental exposures, genetic differences, or both (27).

Because dietary isothiocyanate consumption and lung cancer risk has not been studied in a multi-ethnic population, we evaluated dietary intake assessed by food frequency questionnaire and potential interactions with *GSTM1* genotype in relationship to lung cancer risk in a population-based case-control study of African Americans and Caucasians conducted in Los Angeles County, California.

METHODS

Between 1991 and 1994, incident cases of lung cancer were identified within 7 months of diagnosis from 35 hospitals in Los Angeles County. Controls under age 65 years were randomly selected from licensed drivers who resided in Los Angeles County; while controls over 65 years were randomly selected from lists of Medicare Beneficiaries provided by the Health Care Finance Administration (HCFA). To try and achieve a balance in the distribution between cases and controls for age (within 10 year intervals), race, and gender, controls were frequency matched for these factors to all lung cancer cases diagnosed at the provider hospitals in the previous three years. We attempted to enroll twice as many controls as cases (see London et al 1995 for further details) (28).

Eligibility criteria for the study were as follows: residing in Los Angeles County, being 40–84 years of age, able to complete a questionnaire in English, being Caucasian (non-

Hispanic) or African American, and having had no prior cancer other than nonmelanoma skin cancer. A total of 356 cases and 731 controls were enrolled.

Enrollment consisted of giving a blood sample, and completing an in-person interview about known and possible risk factors for lung cancer. The current analysis was restricted to the 933 subjects (311 cases and 622 controls) who had complete information on smoking, diet, and *GSTM1* genotype measurements.

Study procedures to protect human subjects were approved by the federally designated University of Southern California Institutional Review Board, in accord with assurances approved by the U.S. Department of Health and Human Services. Each subject provided informed consent.

The *GSTM1* genotype was detected by the PCR method described by Zhong et al. (29). This method distinguishes homozygous null from heterozygous and homozygous wild-type and includes an internal control primer for the related but nonpolymorphic *GSTM4* gene. Subject DNA, homozygous wild-type or heterozygous for *GSTM1*, gave PCR products of 230 base pairs (bp) (*GSTM1*) and 157 bp (*GSTM4*), but DNA from homozygous null individuals yielded only the 157-bp *GSTM4* product.

The semi-quantitative food frequency instrument provided information on dietary intake of cruciferous vegetables (30). Cases reported their diet for the year prior to lung-cancer diagnosis, and controls reported their diet for the year prior to their interview date.

Cruciferous vegetable consumption was measured by asking subjects to recall the usual number of servings for the following five types of cruciferous vegetables/dishes separately: broccoli, brussel sprouts, cauliflower, cabbage, and greens. The discrete categories of intake frequencies are: never or less than once per month; 1–3 times per month; 1 time per week; 2–4 times per week; 5–6 times per week; 1 time per day; 2–3 times per day; 4–5 times per day; or 6+ times per day. Responses for each vegetable were assigned the midpoint of the frequency category, transformed to number of servings per month and summarized. Subjects who responded in the uppermost category, 6+ times per day, had their values truncated to 6.0 times per day.

Isothiocyanate content was assigned to three vegetables (broccoli, cauliflower, cabbage) using the transformation constants presented in Jiao et al. (31), and, greens using the transformation constant in Shapiro et al. (32). Both studies used similar phytochemical methods to derive isothiocyanate content. No studies using these methods have derived isothiocyanate content for brussel sprouts, which were rarely consumed among study subjects (mean intake frequency for study population, 11 servings per year) and, therefore were not included in our computation of total dietary isothiocyanate.

We summarized isothiocyanates from each respective cruciferous vegetable into a continuous variable. We constructed approximate quartiles of the summarized isothiocyanate variable based on distribution among the controls (≤25, 26–40, 41–80, > 80μMol); and constructed a median cutpoint of isothiocyanate consumption (40μMol) for stratified analyses.

To provide assurance that dietary isothiocyanates were reflective of underlying cruciferous intake, we also constructed a cruciferous vegetable variable that consisted of summarizing all cruciferous vegetables (broccoli, brussel sprouts, cauliflower, cabbage, and greens). We constructed discrete quartile (approximate) categories of cruciferous vegetable consumption according to number of servings per week (<1, 1, 2 – 3, 4+) based on the control distribution.

Smoking status was established using a reference date: 1 year prior to lung cancer diagnosis for the cases and 1 year plus the median time cases were diagnosed prior to interview date for the controls (15.7 months). Never smokers answered "no," to the question, "Have you smoked 100 cigarettes or more over your lifetime." Subjects who smoked were asked age they started smoking regularly, as well as usual amount smoked.

Unconditional logistic regression models were fitted to the data (33). Odds-ratios and their 95% confidence intervals were estimated using Epilog Plus for Windows, version 1.0 (34).

Smoking was adjusted using a term for the natural logarithm of pack-years and a term for the product of the natural logarithm of years since quitting smoking, as this best characterized the smoking-lung cancer relationship in these data (28). All models included age. Gender and ethnicity were approximate frequency matching factors and were included in all models. Additional factors were included if they changed the estimated effect of the dietary isothiocyanate variable by 10% or more. The final model used to estimate the association between isothiocyanate and lung-cancer risk included terms for ethnicity, gender, smoking history, as well as a continuous term for age.

Terms for saturated fat, occupational exposures, family history, passive smoking, and alcohol fell below the 10% limit of association change between isothiocyanate and lung cancer and therefore were not included. To assess effect modification, we constructed likelihood ratio tests comparing two logistic models: model that contained the constituent variables without the product term; and model that contained the constituent variables plus the product term. We used one-way analysis of variance, and multiple linear regression models adjusted for gender, to compute mean differences of continuous variables and their corresponding p-values. Tests of statistical significance were two-sided. P-values of less than 0.05 were considered significant.

RESULTS

The distribution of gender, ethnicity, smoking status, average age, cruciferous vegetable consumption, dietary isothiocyanate, and polymorphic variants of *GSTM1* are shown in Table 1. The average ages for cases (63.5) and controls (62.6) were very similar (p = 0.22). Distributions for gender and ethnicity differed by 8% and 12% respectively between cases and controls. As expected, smoking patterns were markedly different for cases and controls.

Isothiocyanate intake was inversely associated with lung cancer risk (trend p = 0.02) among the total study population (Table 2). The odds ratio of lung cancer for the uppermost quartile intake category, > 80μMol of isothiocyanate consumption per week, was 0.65 (95% CL = 0.41 – 1.00), adjusted for smoking history and the matching factors. Consumption of cruciferous vegetables (broccoli, cabbage, cauliflower, greens, brussel sprouts) had a corresponding protective association with lung cancer risk (trend p = 0.01). The uppermost intake category of 4+ servings per week of cruciferous vegetables, compared to less than 1 serving per week, was inversely associated with lung cancer risk (OR = 0.60; 95% CL = 0.35 – 1.00) (data not shown).

The isothiocyanate-lung cancer association was stronger among subjects with a *GSTM1* homozygous deletion (OR = 0.52; 95% CL = 0.31 – 0.86) than among those with intact *GSTM1* (OR=0.77; 95% CL = 0.49 – 1.21), but the difference was not statistically significant (P =0.16). The inverse association was slightly stronger in men although power in this group was also greater due to the larger sample size. Differences according to gender were not statistically significant (p=0.18). Although a higher proportion of African-Americans than Caucasians had isothiocyanate intake above the median of 40 units, there was little evidence for a significant difference in the isothiocyanate-lung cancer risk

association between African-Americans and Caucasians (Table 2) (p=0.52). While power for further stratification was limited, there was no evidence that the association between isothiocyanates and lung cancer risk differed by race-sex strata or by race-*GSTM1* strata (data not shown).

There may be a clustering of risk behaviors according to smoking status and gender, with male smokers tending to consume lower amounts of fruits and vegetables (35). Among the controls, male smokers had lower (p = 0.07) mean weekly total ITC consumption (mean = 60.32 μMol) compared to female smokers (mean = 73.53 μMol). When we restricted the sample to smokers we found that males had an adjusted odds ratio of 0.59 (95% CL = 0.39 – 0.89) comparing ITC consumption above the median to consumption below the median whereas the OR for females was 0.72 (95% CL = 0.39 – 1.33). Our sample size did not allow for further stratification, and we could not estimate the effect of ITC according to the *GSTM1* genotype by smoking and gender.

Table 3 shows average servings per week of cruciferous vegetables (overall, and for each vegetable type) according to race among the control subjects. African Americans had a higher average number of servings per week of total cruciferous vegetables than Caucasians (p = 0.02). In particular, intakes of greens (p= 0.0001) and cabbage (p=0.004) were greater in African Americans.

DISCUSSION

We found a protective effect of isothiocyanate intake on lung cancer risk in our study of African-Americans and Caucasians. In addition, the protective effect of higher isothiocyanate intake was greater among individuals with genetic deficiency of *GSTM1*. These results are in agreement with our previous findings from a prospective study of men in Shanghai, China (17), and from our case-control study of Chinese women in Singapore (19). Similar results have been seen in other studies, both case-control and cohort (18, 20,21).

We observed similar associations for isothiocyanate and lung-cancer risk among African Americans and Caucasians. Over the past several years, population-based research has examined risk factors that might help to explain the elevated lung cancer incidence among African Americans (28, 36–39). Results from this study are compatible with the published literature and suggest that dietary factors do not explain the excess incidence among African-Americans (1,2,38).

We observed a stronger inverse association between isothiocyanate intake and lung cancer among subjects with the homozygous deletion of *GSTM1*, consistent with previous studies (17–21), although the difference did not achieve statistical significance. Several focused experimental and clinical studies have provided biological evidence for the GST-isothiocyanate interaction. Animal studies have shown isothiocyanate to be a potent inhibitor of lung carcinogenesis induced by tobacco carcinogens such as NNK (nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone), and PAHs (polycyclic aromatic hydrocarbons) (15, 40–42). This inhibition effect is stronger when phase II enzymes such as *GSTM1* are functionally de-activated, possibly resulting in longer circulating half-lives of isothiocyanate and thus a greater degree of chemoprevention (43). Isothiocyanates also have been shown to inhibit carcinogenesis by induction of apoptosis (44) or protection against oxidative damage (45).

The ITC association we observed may have resulted from foods that are likely to be eaten along with cruciferous vegetables such as fruits, beta carotene, vitamin C, or vegetables that are rich in beta carotene and other protective nutrients. To address whether our results were

due to these potential confounding factors, we adjusted the ITC and lung cancer risk model for all fruits, and orange, yellow, and red vegetables. Likewise, we adjusted the model for beta carotene and vitamin C. For both models, adjustment for these factors made no appreciable difference on the ITC associations with lung cancer risk that we observed.

Our study has several potential limitations. Responses to the food frequency questionnaire regarding consumption of cruciferous vegetables from the cases may have been influenced by their lung cancer diagnosis. However, our interviews were conducted face-to-face at subjects' homes by trained interviewers who were instructed to prompt the subjects repeatedly to recall their diets one-year prior to diagnosis for the cases and equivalent dates for controls. Further, the associations we observed between isothiocyanate and lung cancer risk are comparable to those of previous studies, both case-control (18–20) and cohort studies (21), suggesting that reporting biases were minimal with respect to cruciferous vegetable consumption.

We may have underestimated total isothiocyanate consumption because not all cruciferous vegetables were present on our questionnaire. For instance, we did not include watercress on our questionnaire. Watercress consumption is common in Asian countries but not in the United States (46). Because we studied both African Americans and Caucasians residing in Los Angeles, we used a food frequency questionnaire that, at the time, was likely to capture representative foods consumed by both racial groups (30). We asked about greens in our study, but did not ask about watercress. While watercress has the highest isothiocyanate concentration of cruciferous vegetables (47), because it is uncommonly consumed in the United States, having watercress present on the food frequency questionnaire probably would not have made a difference in our calculation of total ITC consumption.

Theoretically, selection bias could have influenced the isothiocyanate association if participation by case-control status was differential based on cruciferous vegetable consumption. Smokers are known to consume lower amounts of fruits and vegetables than non-smokers (48), and smoking could have influenced study participation. To address possible selection bias, we collected smoking information for potential controls that did not participate in the full study (see SJ London et al, Carcinogenesis for more details) (49). The proportion of ever smokers among the 121 nonparticipants that answered the abbreviated questionnaire (61%) resembled the proportion of ever smokers in the enrolled control group (66%). The small difference in smoking prevalence between the non-respondents and the participating controls suggests that the selective sampling of eligible controls had minimal influence on the results.

Our results confirm those reported by other population-based studies of dietary isothiocyanate, *GSTM1* genotype, and lung cancer risk. Our study is the first to report dietary isothiocyanate in relationship to lung-cancer risk among African Americans.

To summarize, we found a protective association for dietary isothiocyanate consumption in relation to lung cancer. We did not find that the isothiocyanate association varied according to whether subjects were African American or Caucasian. The association was greater among individuals lacking in *GSTM1* activity by virtue of homozygous deletion. Our results support recent data suggesting that genetic variation in the metabolism of anti-carcinogens contained in food may be important in the development of lung cancer.

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References

1. Fontham ET, Pickle LW, Haenszel W, Correa P, Lin YP, Falk RT. Dietary vitamins A and C and lung cancer risk in Louisiana. Cancer. 1988; 62:2267–2273. [PubMed: 3179940]
2. Dorgan JF, Ziegler RG, Schoenberg JB, Hartge P, McAdams MJ, et al. Race and sex differences in associations of vegetables, fruits, and carotenoids with lung cancer risk in New Jersey (United States). Cancer Causes and Control. 1993; 4:273–281. [PubMed: 8318643]
3. Ziegler RG, Mason TJ, Stemhagen A, Hoover R, Schoenberg JB, et al. Dietary carotene and vitamin A and risk of lung cancer among white men in New Jersey. J Natl Cancer Inst. 1984; 73:1429–1435. [PubMed: 6595451]
4. Ziegler RG, Mason TJ, Stemhagen A, Hoover R, Schoenberg JB, et al. Carotenoid intake, vegetables, and the risk of lung cancer among white men in New Jersey. Am J Epidemiol. 1986; 123:1080–1093. [PubMed: 3706278]
5. LeMarchand L, Yoshizawa CN, Kolonel LN, Hankin JH, Goodman MT. Vegetable consumption and lung cancer risk: A population-based case-control study in Hawaii. J Natl Cancer Inst. 1989; 81:1158–1164. [PubMed: 2545891]
6. Taylor-Mayne S, Janerich DT, Greenwald P, Chorost S, Tucci C, et al. Dietary beta-carotene and lung cancer risk in U.S. nonsmokers. J Natl Cancer Inst. 1994; 86:33–38. [PubMed: 8271280]
7. Speizer FE, Colditz GA, Hunter DJ, Rosner B, Hennekens C. Prospective study of smoking, antioxidant intake, and lung cancer in middle-aged women (USA). Cancer Causes and Control. 1999; 10:475–482. [PubMed: 10530619]
8. Ziegler RG, Subar AF, Craft NE, Ursin G, Patterson BH, et al. Does β-carotene explain why reduced cancer risk is associated with vegetable and fruit intake? Cancer Res Suppl. 1992; 52:2060s–2066s.
9. Neuhouser ML, Patterson RE, Thornquist MD, Omenn GS, King IB, et al. Fruits and vegetables are associated with lower lung cancer risk only in the placebo arm of the beta-carotene and retinol efficacy trial (CARET). Cancer Epidemiol Biomarkers Prev. 2003; 12:350–358. [PubMed: 12692110]
10. Feskanich D, Ziegler RG, Michaud DS, Giovannucci EL, Speizer FE, et al. Prospective study of fruit and vegetable consumption and risk of lung cancer among men and women. J Natl Cancer Inst. 2000; 92:1812–1823. [PubMed: 11078758]
11. Verhoeven DT, Goldbohm RA, van Poppel G, Verhagen H, van den Brandt PA. Epidemiological studies on *Brassica* vegetables and cancer risk. Cancer Epidemiol Biomark Prev. 1996; 5:733–748.
12. Smith-Warner SA, Spiegelman D, Yaun S-S, Albanes D, Beeson WL, et al. Fruits, vegetables and lung cancer: A pooled analysis of cohort studies. Int J Cancer. 2003; 107:1001–1011. [PubMed: 14601062]
13. Miller AB, Altenburg H-P, Mesquita BB, Boshuizen HC, Aguido A, et al. Fruits and vegetables and lung cancer: Findings from the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2004; 108:269–276. [PubMed: 14639614]

14. Steinmetz KA, Potter JD. Vegetables fruit and cancer II. Mechanisms. Cancer Causes Control. 1991; 2:427–442. [PubMed: 1764568]
15. Hecht SS. Inhibition of carcinogenesis by isothiocyanates. Drug Metab Rev. 2000; 32:395–411. [PubMed: 11139137]
16. Conaway CC, Wang C-X, Pittman B, Yang Y-M, Schwartz JE, et al. Phenethyl isothiocyanate and sulforaphane and their N-acetylcysteine conjugates inhibit malignant progression of lung adenomas induced by tobacco carcinogens in A/J mice. Cancer Res. 2005; 65:8548–8557. [PubMed: 16166336]
17. London SJ, Yuan J-M, Chung F-L, Gao Y-T, Coetzee GA, et al. Isothiocyanates, glutathione S-transferase M1 and T1 polymorphisms, and lung-cancer risk: a prospective study of men in Shanghai, China. Lancet. 2000; 356:724–729. [PubMed: 11085692]
18. Spitz MR, Duphorne CM, Detry MA, Pillow PC, Amos CI, et al. Dietary intake of isothiocyanates: evidence of a joint effect with glutathione S-transferase polymorphisms in lung cancer risk. Cancer Epidemiol Biomark Prev. 2000; 9:1017–1020.
19. Zhao B, Seow A, Lee EJD, Poh WT, Eng P, et al. Dietary isothiocyanates, glutathione S-transferase –M1, -T1 polymorphisms and lung cancer risk among Chinese women in Singapore. Cancer Epidemiol Biomarkers Prev. 2001; 10:1063–1067. [PubMed: 11588132]
20. Brennan P, Hsu CC, Moullan N, Szeszenia-Dabrowska N, Lissowska J, et al. Effect of cruciferous vegetables on lung cancer in patients stratified by genetic status: a mendelian randomization approach. The Lancet. 2005; 366:1558–1560.
21. Lewis S, Brennan P, Nyberg F, Ahrens W, Constantinescu V, et al. Cruciferous vegetable intake, *GSTM1* genotype and lung cancer risk in a non-smoking population. In, Riboli E and Lambert R, eds, *Nutrition and Lifestyle: Opportunities for Cancer Prevention*. Lyon, France. IARC Scientific Publications. 2002; 156:507–508. [PubMed: 12484246]
22. Wang LI, Giovannucci EL, Hunter D, Neuberg D, Su L, et al. Dietary intake of cruciferous vegetables, Glutathione S-transferase (GST) polymorphisms and lung cancer risk in a Caucasian population. Cancer Causes Control. 2004; 15:977–985. [PubMed: 15801482]
23. Sorensen M, Raaschou-Nielsen O, Brasch-Andersen C, Tjonneland A, Overvad K, et al. Interactions between GSTM1, GSTT1 and GSTP1 polymorphisms and smoking and intake of fruit and vegetables in relation to lung cancer. Lung Cancer. 2007; 55:137–144. [PubMed: 17123660]
24. Tucker KL, Maros J, Champagne C, Connell C, Goolsby S, et al. A regional food-frequency questionnaire for the US Mississippi Delta. Public Health Nutr. 2005; 8:87–96. [PubMed: 15705249]
25. Ries, LAG.; Harkins, D.; Krapcho, M.; Mariotto, A.; Miller, BA., et al. [Accessed May, 2008] SEER Cancer Statistics Review, 1975–2003. SEER data submission posted to the SEER web site 2006. Nov. 2005 http://seer.cancer.gov/csr/1975_2004/
26. Haiman CA, Stram DO, Wilkens LR, Pike MC, Kolonel LN, et al. Ethnic and racial differences in the smoking-related risk of lung cancer. N Engl J Med. 2006; 354:333–342. [PubMed: 16436765]
27. Risch N. Dissecting racial and ethnic differences. N Engl J Med. 2006; 354:408–410. [PubMed: 16436773]
28. London SJ, Daly AK, Cooper J, Navidi WC, Carpenter CL, et al. Polymorphism of glutathione S-transferase M1 (*GSTM1*) and the risk of lung cancer among African Americans and Caucasians in Los Angeles County. J Natl Cancer Inst. 1995; 87:1246–1253. [PubMed: 7563171]
29. Zhong S, Wyllie AH, Barnes D, Wolf CR, Spurr NK. Relationship between the *GSTM1* genetic polymorphism and susceptibility to bladder, breast and colon cancer. Carcinogenesis. 1993; 14:1821–1824. [PubMed: 8403204]
30. Willett WC, Sampson L, Browne ML, Stampfer MJ, Rosner B, et al. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol. 1988; 127:188–199. [PubMed: 3337073]
31. Jiao D, Yu MC, Hankin JH, Low S-H, Chung F-L. Total isothiocyanate contents in cooked vegetables frequently consumed in Singapore. J Agric Food Chem. 1998; 46:1055–1058.
32. Shapiro TA, Fahey JW, Wade KL, Stephenson KK, Talalay P. Human metabolism and excretion of cancer chemoprotective glucosinolates and isothiocyanates of cruciferous vegetables. Cancer Epidemiol Prev. 1998; 7:1091–1100.

33. Breslow, NE.; Day, NE. The analysis of case-control studies. Vol. 1. Lyon, France: International Agency for Research on Cancer; 1980. Statistical methods in cancer research. Publications No. 32
34. Epicenter Software. EPILOG for Windows. Pasadena; CA: 1999.
35. Park S-Y, Murphy SP, Wilkens LR, Yamamoto JF, Sharma S, Hankin JH, Henderson BE, Kolonel LN. Dietary patterns using the food guide pyramid groups are associated with sociodemographic and lifestyle factors: the Multiethnic Cohort study. J Nutr. 2005; 135:843–849. [PubMed: 15795445]
36. Stellman SD, Chen Y, Muscat JE, Diordievic MV, Richie JP Jr, et al. Lung-cancer risk in white and black Americans. Ann Epidemiol. 2003; 4:294–302. [PubMed: 12684197]
37. Wu X, Zhao H, Amos CI, Shete S, Makan N, et al. p53 genotypes and haplotypes associated with lung cancer susceptibility and ethnicity. J Natl Cancer Inst. 2002; 94:681–690. [PubMed: 11983757]
38. Pillow PC, Hursting SD, Duphorne CM, Jiang H, Honn SE, et al. Case-control assessment of diet and lung cancer risk in African Americans and Mexican Americans. Nutr Cancer. 1997; 29:169–173. [PubMed: 9427982]
39. Carpenter CL, Jarvik ME, Morgenstern H, McCarthy WJ, London SJ. Mentholated cigarette smoking and lung cancer risk. Ann Epidemiol. 1999; 9:114–120. [PubMed: 10037555]
40. Chung F-L, Morse MA, Eklind KI. New potential chemopreventive agents for lung carcinogenesis of tobacco-specific nitrosamine. Cancer Res. 1992; 52(Suppl):2719s–2722s. [PubMed: 1563003]
41. Zhang Y, Talalay P. Anticarcinogenic activities of organic isothiocyanates: chemistry and mechanisms. Cancer Res. 1994; 54(Suppl):1976s–1981s. [PubMed: 8137323]
42. Chung F-L, Kelloff G, Steele V, Pittman B, Zang E, et al. Chemopreventive efficacy of arylalkyl isothiocyanates and N-acetylcysteine for lung tumorigenesis in Fischer rats. Cancer Res. 1996; 56:772–778. [PubMed: 8631012]
43. Lampe JW, Peterson S. Brassica, biotransformation and cancer risk: genetic polymorphisms alter the preventive effects of cruciferous vegetables. J Nutr. 2002; 132:2991–2994. [PubMed: 12368383]
44. Yu R, Mandlekar S, Harvey KJ, Ucker DS, Kong AN. Chemopreventive isothiocyanates induce apoptosis and caspase-3-like protease activity. Cancer Res. 1998; 58:402–408. [PubMed: 9458080]
45. Verhagen H, deVries A, Nijhoff WA, Schouten A, van Poppel G, Peters WH, et al. Effects of Brussel sprouts on oxidative DNA-damage in man. Cancer Lett. 1997; 114:127–30. [PubMed: 9103270]
46. International Agency for Research on Cancer. Cruciferous vegetables. Vol. 9. IARC Press. World Health Organization; Lyon France: 2004.
47. Seow A, Shi C-Y, Chung F-L, Jiao D, Hankin JH, et al. Urinary total isothiocyanate (ITC) in a population-based sample of middle-aged and older Chinese in Singapore: Relationship with dietary total ITC and glutathione S-transferase *M1/T1/P1* genotypes. Cancer Epid Biomark Prev. 1998; 7:775–781.
48. Vainio, H.; Bianchini, F., editors. IARC Working Group on Evaluation of Cancer Preventive Strategies. Fruits and vegetables. Vol. 8. Lyon France: IARC Handbook of Cancer Prevention; International Agency for Research on Cancer; 2003.
49. London SJ, Daly AK, Leathart JB, Navidi WC, Carpenter CC, et al. Genetic polymorphism of CYP2D6 and lung cancer risk in African-Americans and Caucasians in Los Angeles County. Carcinogenesis. 1997; 18:1203–1214. [PubMed: 9214604]

Table 1

Selected variables that describe the study population

		Cases		Controls	
Variable	**Category**	**N**	**%**	**N**	**%**
Cruciferous Vegetables[1]					
	<1 serving per week	50	16.1	77	12.4
	1 serving per week	97	31.2	170	27.3
	2–3 servings per week	78	25.1	178	28.6
	4+ servings per week	86	27.7	197	31.7
Dietary Isothiocyanates					
	≤ 25 μMol	91	29.3	146	23.5
	26 – 40 μMol	66	21.2	121	19.5
	41 – 80 μMol	74	23.8	173	27.8
	> 80 μMol	80	25.7	182	29.3
GSTM1					
	wild type	184	59.2	346	55.6
	homozygous null	127	40.8	276	44.4
Race					
	Caucasian (non Hispanic White)	172	55.3	424	68.2
	African American	139	44.7	198	31.8
Sex					
	female	130	41.8	205	33.0
	male	181	58.2	417	67.0
Smoking Status					
	never smoker	10	3.2	213	34.2
	former smoker	103	33.1	276	44.4
	current smoker	198	63.7	133	21.4
Age in years, mean/median, (SD)		63.52/64.0	(9.38)	62.57/63.0	(8.43)

[1] Cruciferous vegetables include broccoli, cabbage, cauliflower, greens, and brussel sprouts

Table 2

Odds ratios and 95% confidence intervals for dietary isothiocyanate (ITC) effect on lung cancer risk for total population, and population by glutathione S-transferase M1 (GSTM1), smoking, gender, and race.

Variable Category	ITC Category	Cases	Controls	Adjusted[1] OR	Adjusted[2] OR	95% CL	p -value
Total Population							
	≤ 25 μMol	91	146	1.00	1.00	----------	
	26 – 40 μMol	66	121	0.85	0.84	(0.53 – 1.35)	
	41 – 80 μMol	74	173	0.58	0.53	(0.34 – 0.84)	
	> 80 μMol	80	182	0.57	0.65	(0.41 – 1.00)	
test for trend							0.02
GSTM1=wild type							
	[3]< 40 μMol	86	150	1.00	1.00	----------	
	≥ 40 μMol	98	196	0.72	0.77	(0.49 – 1.21)	
GSTM1=homozygous null							
	< 40 μMol	70	117	1.00	1.00	----------	
	≥ 40 μMol	57	159	0.53	0.52	(0.31 – 0.86)	
test for homogeneity[4]							0.16
Ever Smokers							
	< 40 μMol	153	187	1.00	1.00	----------	
	≥ 40 μMol	148	222	0.65	0.63	(0.45 – 0.89)	
male[5]							
	< 40 μMol	107	196	1.00	1.00	----------	
	≥ 40 μMol	74	221	0.56	0.57	(0.38 – 0.86)	
Female							
	< 40 μMol	49	71	1.00	1.00	----------	
	≥ 40 μMol	81	134	0.76	0.81	(0.46 – 1.45)	
test for homogeneity							0.18
African American[6]							
	< 40 μMol	59	62	1.00	1.00	----------	
	≥ 40 μMol	80	136	0.54	0.54	(0.32 – 0.92)	
Caucasian							

Variable Category	ITC Category	Cases	Controls	Adjusted[1] OR	Adjusted[2] OR	95% CL	p -value
	< 40 μMol	97	205	1.00	1.00	----------	
	≥ 40 μMol	75	219	0.69	0.72	(0.47 – 1.11)	
test for homogeneity							0.52

[1] Adjusted for matching factors: age, ethnicity, gender.

[2] Adjusted for matching factors, natural logarithm of pack years plus natural logarithm of years since quitting multiplied by natural logarithm of pack years.

[3] Dietary ITC consumption divided at medial value among controls.

[4] Test for homogeneity reflects log likelihood ratio tests of model with product term evaluated against model without product term

[5] Term for gender omitted from model.

[6] Term for ethnicity omitted from model.

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Table 3

Average Servings per Week of Cruciferous Vegetables[1] according to Race among Healthy Controls

		African American				Caucasians			
Cruciferous Vegetable	**N**	**Mean**	**Median**	**Std Dev**	**N**	**Mean**	**Median**	**Std Dev**	**Adjusted p-value[2]**
	198				**424**				
Broccoli		1.30	1.00	1.51		1.29	1.00	1.38	0.82
Cabbage		1.08	0.50	1.21		0.79	0.50	1.11	0.004*
Cauliflower		0.53	0.00	1.15		0.68	0.50	0.99	0.10
Greens		0.63	0.50	0.87		0.09	0.00	0.41	0.0001*
Brussel Sprouts		0.20	0.00	0.47		0.25	0.00	0.63	0.33
Total Cruciferous[1]		3.74	2.50	3.61		3.10	2.00	3.09	0.02*

[1] Cruciferous vegetables include broccoli, cabbage, cauliflower, brussel sprouts, and greens

[2] Adjusted for gender

* p-value ≤ 0.05