Research Article

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Glycemic Index, Glycemic Load, and Lung Cancer Risk in Non-Hispanic Whites

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Abstract

Background: Postprandial glucose (PPG) and insulin responses play a role in carcinogenesis. We evaluated the association between dietary glycemic index (GI) and glycemic load (GL), markers of carbohydrate intake and PPG, and lung cancer risk in non-Hispanic whites.

Methods: GL and GI were assessed among 1,905 newly diagnosed lung cancer cases recruited from the University of Texas MD Anderson Cancer Center (Houston, TX) and 2,413 healthy controls recruited at Kelsey-Seybold Clinics (Houston, TX). We assessed associations between quintiles of GI/GL and lung cancer risk and effect modification by various risk factors. ORs and 95% confidence intervals (CI) were estimated using multivariable logistic regression.

Results: We observed a significant association between GI [5th vs. 1st quintile (Q) OR = 1.49; 95% CI, 1.21–1.83; P_{trend} <0.001] and lung cancer risk and GI_{ac} (5th vs. 1st Q OR = 1.48; 95% CI, 1.20–1.81; P_{trend} = 0.001) and lung cancer risk. We observed a more pronounced association between GI and lung cancer risk among never smokers (5th vs. 1st Q OR = 2.25; 95% CI, 1.42–3.57), squamous cell carcinomas (SCC; 5th vs. 1st Q OR = 1.92; 95% CI, 1.30–2.83), and those with less than 12 years of education (5th vs. 1st Q OR = 1.75; 95% CI, 1.19–2.58, $P_{interaction}$ = 0.02).

Conclusion: This study suggests that dietary GI and other lung cancer risk factors may jointly and independently influence lung cancer etiology.

Impact: Understanding the role of GI in lung cancer could inform prevention strategies and elucidate biologic pathways related to lung cancer risk. *Cancer Epidemiol Biomarkers Prev; 25(3); 532–9. ©2016 AACR.*

Introduction

Lung cancer is the second most commonly diagnosed cancer in the United States (1). Smoking is the most well-characterized risk factor for lung cancer and accounts for approximately 85% of the population burden of lung cancer in developed nations (2). However, evidence suggests that select dietary factors may modulate lung cancer risk. Factors including vitamins A, C, and E and diets high in fruits and vegetables have been associated with reduced lung cancer risk, whereas intake of red meat, dairy products, saturated fat, and lipids have all been associated with an increased risk (3).

The type and amount of dietary carbohydrate are the main determinants of postprandial glucose and insulin responses (4) which have been shown to play a role in promoting tumor growth and carcinogenesis (5, 6). The glycemic index (GI) is a classification of carbohydrate-rich foods based on postprandial blood glucose responses, dependent on both the nature of the carbohydrate and the type and extent of the food processing. GI measures how quickly carbohydrates in food cause blood glucose levels to rise after eating (7). Elevated blood glucose levels stimulate the secretion of insulin. Insulin receptors activate signaling pathways in the cell that are mitogenic, suggesting that chronically elevated concentrations of insulin may influence the risk of cancer through indirect effects on the insulin-like growth factors (IGF). IGFs have been shown to play a critical role in regulating cell proliferation and differentiation in cancer (8) and there is evidence to suggest that IGFs are elevated in lung cancer patients (9, 10).

Previous studies have investigated the association between GI, and the related measure glycemic load (GL), and a variety of cancers including colorectal (11–13), stomach (14–16), pancreas (17, 18), endometrial (7, 19–21), ovarian (22, 23), prostate (24, 25), and thyroid (26) but these studies are limited and results have been largely inconclusive. To date, only one smaller study has evaluated the association between dietary GI and lung cancer risk in a case–control population in Uruguay (27). In a large study of newly diagnosed lung cancer patients and healthy controls, we investigated whether dietary GI and GL were associated with lung cancer risk in non-Hispanic whites, and whether these associations varied by known or suspected lung cancer risk factors, including smoking.

Materials and Methods

Study population

The patients and control subjects were selected from an ongoing case–control study of lung cancer conducted in the

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Department of Epidemiology at The University of Texas MD Anderson Cancer Center. Newly diagnosed, histologically confirmed cases who had not previously received treatment other than surgery were recruited from MD Anderson Cancer. Healthy control subjects, with no previous history of cancer (except nonmelanoma skin cancer), were selected from individuals seen for routine care at Kelsey-Seybold Clinics; the largest physician group-practice plan in the Houston Metropolitan area. Controls were frequency matched to cases according to their age in 5-year categories, gender, and ethnicity. The study was approved by the Institutional Review Boards at The University of Texas MD Anderson Cancer Center and the Kelsey-Seybold Foundation.

Data collection

All study participants completed an in-person interview by MD Anderson staff interviewers to obtain information on a variety of factors, including but not limited to, demographics, socioeconomic status (education), history of hypertension prior to diagnosis or recruitment (for control subjects), physical activity and smoking (including cigarettes per day), and alcohol history. An individual who had never smoked or had smoked less than 100 cigarettes in his or her lifetime was defined as a never smoker. An individual who had smoked at least 100 cigarettes in his or her lifetime but had quit at least 12 months prior to diagnosis (for cases) or interview (for controls) was classified as a former smoker. Current smokers were those who were currently smoking or quit less than 12 months before diagnosis (for cases) or before the interview (for controls).

Weight and height at diagnosis (for cases) or recruitment (for control subjects) was recorded. Body mass index (BMI; kg/m^2) was derived from adult weight and height. BMI was categorized according to the standard classifications of the World Health Organization (WHO; normal = <25 kg/m^2; overweight = 25–29.9 kg/m^2; obese = ≥30 kg/m^2). Participants also reported the average number of times they undertook each of the five broad groups of activities in the year before the interview. Activities included active sports, physical exercises, swimming, walking (including walking for golf), cycling, gardening or yard work, hunting, housework, and other strenuous exercises. A metabolic equivalent value (MET) was assigned on the basis of the energy cost of each activity group (28). Energy expenditure from physical activity was calculated as the MET value of each activity multiplied by the frequency of each activity and then summed across all activities.

We used a modified version of the NCI Health Habits and History Questionnaire (29). The questionnaire includes a semiquantitative food frequency list made up of food and beverage items and an open-ended section regarding dietary behaviors such as dining in restaurants and food preparation methods. Portion size was also queried. Total energy intake, total carbohydrate intake, total fiber intake, and grams per day of consumption for each food item were estimated using the USDA Food and Nutrient Database for Dietary Studies (30). Total meat intake was calculated by adding total grams per day of each meat item in the food frequency questionnaire (FFQ). All nutrient and food variables of interest were energy adjusted for total caloric intake using the residual method (31).

Because of smaller numbers of minorities, the large number of GI/GL categories, and to reduce the residual confounding by population stratification, the current analysis is limited to non-Hispanic whites only.

Exclusions and eligibility

A total of 4,644 non-Hispanic white cases and controls had complete dietary information for inclusion in the current analysis. We excluded individuals with outlying total energy intake by excluding individuals ($N = 158$) with values that fell outside the interval delimited by the 25th percentile minus 1.5 times the interquartile range and the 75th percentile plus 1.5 times the interquartile range based on the distribution of energy intake in the population, by gender. Individuals with missing BMI were excluded from the analysis as the distribution of missing data was not even among cases and controls ($N = 168$). A total of 4,318 individuals were included in the current analysis (1,905 cases and 2,413 controls).

GI/load calculations

We derived GI values according to a method previously described (32, 33). Briefly, using published GI values compiled by Foster-Powell and colleagues (32), we linked GI values (using a scale in which the GI for pure glucose = 100) to each of the individual foods in the FFQ. The overall GL was calculated by taking the product of the carbohydrate content of a given food item by the quantity of that food item consumed per day and its GI value and then summing the values for all food items. The overall GI, which reflects the average quality of carbohydrate consumed, was calculated by dividing the total GL by total daily carbohydrate consumption. We also calculated total GI using total available carbohydrate (GI_{ac}), which was calculated using the same formula for GI, but by subtracting the fiber values from the carbohydrate values used in the GI calculations. GI exposures were energy-adjusted using the residual method (31).

Statistical analysis

Physical activity levels (METs) and alcohol intake were categorized into tertiles based on the distribution in control subjects. Missing physical activity was consistent between cases and controls and therefore coded as a separate "unknown" category. Analyses limited to only the sample with complete physical activity information were consistent with the overall findings. Smoking status was categorized according to pack-years, calculated as the number of cigarettes per day multiplied by the number of years smoking, into the following categories: never smoker, former smoker <20 pack-years, former smoker ≥ 20 pack-years, current smoker < 20 pack-years, and current smoker ≥ 20 pack-years. We additionally created a more granular categorization of smoking (never smoker, former smoker <10 pack-years, former smoker 10–20 pack-years, former smoker ≥ 20 pack-years, current smoker < 10 pack-years, current smoking 10–20 pack-years, and current smoker ≥ 20 pack-years) which yielded consistent results (not shown). Alcohol consumption was adjusted for total caloric intake using the residual method and divided into tertiles based on the distribution in the controls for males and females separately. GI and GL exposures were categorized into quintiles based on the distribution among the controls and by gender with the reference group comprised of individuals in the lowest category of intake.

Comparisons for case–control characteristics were performed using the Pearson χ^2 test for categorical variables and Student t tests for continuous variables. Unconditional logistic regression was used to calculate OR and 95% confidence intervals (CI) for the association between quintiles of GI and GL and lung cancer

risk [overall and separately for two major histologic subtypes, adenocarcinoma (AC) and squamous cell carcinoma (SCC)]. In calculating ORs and 95% CIs, we used two modeling approaches. In the first (minimally adjusted) model, we included age, gender, education (<12 years, 12–15 years, 16+ years), and smoking status. Matching variables were retained in these models to account for the possibility of residual confounding.

In the second approach (the fully adjusted model), we additionally controlled for variables that were considered biologically and statistically relevant in the multivariable model. Variables were retained if they improved the fit and predictive power of the model and were statistically significant by the likelihood ratio test. The variables included physical activity (tertiles), BMI (WHO categories), total caloric intake (continuous), alcohol intake (tertiles), total meat intake (energy-adjusted continuous), and fiber intake (energy-adjusted continuous). Alcohol intake, meat intake, and fiber intake were removed from the final model because they were not associated with lung cancer risk. Tests for trend were obtained by including an ordinal exposure variable in the model.

Stratified analyses for overall lung cancer risk were conducted by smoking status (never/ever), gender, years of education (<12, 12+), age (<60, 60+), and BMI (normal vs. overweight and obese). Multiplicative interaction was assessed by including the cross-product term of dichotomous variable with the GI/GL exposure in the logistic regression model. Statistical significance was determined using the Wald statistic. We subsequently ran a sensitivity analysis on a dataset further matched on smoking status. Results of this analysis were qualitatively similar to the overall findings and are presented in the Supplementary Tables S1–S3. Joint effects of smoking (ever/never) and GL/GI (median high/low, determined by the distribution in controls, by

Table 1. Participant characteristics

	Cases ($N = 1{,}905$) **N (%)**	**Controls ($N = 2{,}413$)** **N (%)**	***P***
Age, mean (SD)[a]	60.69 (10.67)	60.78 (10.43)	0.79
Gender[a]			
Male	1,006 (52.81)	1,232 (51.06)	
Female	899 (47.19)	1,181 (48.94)	0.25
Smoking status			
Never	311 (16.33)	593 (24.58)	
Former	814 (42.73)	988 (40.94)	
Current	780 (40.94)	832 (34.48)	<0.001
Pack-years in ever smokers, mean (SD)	49.85 (31.00)	42.32 (30.33)	<0.001
BMI, kg/m^2			
Underweight/normal	841 (44.15)	774 (32.08)	
Overweight	688 (36.12)	955 (39.58)	
Obese	376 (19.74)	684 (28.35)	<0.001
Physical activity[b]			
Low	618 (39.34)	666 (31.28)	
Medium	460 (29.28)	649 (30.48)	
High	493 (31.38)	814 (38.23)	<0.001
Years of education[b]			
< 12	792 (41.62)	603 (25.03)	
12–15	558 (29.32)	825 (34.25)	
16+	553 (29.06)	981 (40.72)	<0.001
Family history of cancer[b]			
No	1,442 (76.97)	2,016 (83.90)	
Yes	456 (24.03)	387 (16.10)	0.001
Emphysema[b]			
No	1,547 (82.11)	2,250 (93.36)	
Yes	337 (17.89)	160 (6.64)	<0.001
Pneumonia[b]			
No	1,114 (58.94)	1,717 (71.30)	
Yes	776 (41.06)	691 (28.70)	<0.001
Hay fever[b]			
No	1,591 (84.63)	1,897 (78.68)	
Yes	289 (15.37)	514 (21.32)	<0.001
Histologic subtype[c]			
Adenocarcinoma	1,071 (57.06)	NA	
SCC	446 (23.76)	NA	
Other	360 (19.18)	NA	
Dietary factors			
GL, mean (SD)	136.64 (62.86)	136.77 (56.86)	0.94
GI, mean (SD)	53.75 (5.14)	52.74 (4.30)	<0.001
GI, available carbohydrate, mean (SD)	58.33 (5.22)	57.62 (4.31)	<0.001
Carbohydrate g/day, mean (SD)	252.09 (110.59)	258.03 (101.65)	0.06
Fiber g/day, mean (SD)	19.19 (9.46)	21.39 (10.05)	<0.001
Meat intake g/day, mean (SD)	125.94 (81.08)	127.09 (74.50)	0.63

[a]Matching factors.

[b]Missing: years of education, $N = 6$; family history of cancer, $N = 17$; emphysema, $N = 24$; pneumonia, $N = 20$; hay fever, $N = 27$; unknown physical activity, $N = 618$.

[c]Unknown histologic subtype not included in the table ($N = 28$).

gender) were also assessed. Analyses were conducted with STATA version 13.0 (Stata Corp).

Results

Participant characteristics are described in Table 1. Cases were more likely to smoke, be heavier smokers and had lower BMI, physical activity levels, and years of education ($P < 0.001$ each). Cases had higher daily values for both GI variables ($P < 0.001$ for each), lower total carbohydrate intake grams per day (marginally significant $P = 0.06$), and lower fiber intake ($P < 0.001$).

Minimally and fully adjusted results for the association between GI and GL variables and lung cancer risk (overall, AC, and SCC) are presented in Table 2. GL was not associated with lung cancer risk in any model. Higher GI and GI_{ac} were significantly associated with an increased risk of lung cancer overall (GI 5th vs. 1st quintile, fully adjusted OR = 1.49; 95% CI, 1.21–1.83; $P_{trend} < 0.001$; GI_{ac} 5th vs. 1st quintile, fully adjusted OR = 1.48; 95% CI, 1.20–1.81; $P_{trend} = 0.001$). GI_{ac} was marginally significantly associated with AC risk (GI_{ac} 5th vs. 1st quintile, fully adjusted OR = 1.31; 95% CI, 1.02–1.67; $P_{trend} = 0.08$). GI and GI_{ac} were significantly associated with SCC risk (GI 5th vs. 1st quintile, fully adjusted OR = 1.92; 95% CI, 1.30–2.83; $P_{trend} < 0.001$; GI_{ac} 5th vs. 1st quintile, fully adjusted OR = 1.92; 95% CI, 1.31–2.82; $P_{trend} < 0.001$), with more pronounced effect estimates for SCCs compared with ACs.

Analyses stratified by age, gender, education, smoking status, and BMI were also conducted (Table 3). Effect estimates for GL, GI, and GI_{ac} were more pronounced for never smokers compared with ever smokers (GL 5th vs. 1st quintile; never smokers OR = 1.81; 95% CI, 1.11–2.93; $P_{trend} = 0.02$ vs. ever smokers OR = 1.01; 95% CI, 0.80–1.26; $P_{trend} = 0.94$, GI 5th vs. 1st quintile; never smokers OR = 2.25; 95% CI, 1.42–3.59; $P_{trend} = 0.002$ vs. ever smokers OR = 1.31; 95% CI, 1.04–1.65; $P_{trend} = 0.02$, GI_{ac} 5th vs. 1st quintile, never smokers OR = 2.06; 95% CI, 1.30–3.27; $P_{trend} = 0.001$ vs. ever smokers OR = 1.36; 95% CI, 1.08–1.71; $P_{trend} = 0.01$). A significant interaction was observed between GL and smoking status ($P_{interaction} = 0.04$).

Table 2. Associations between lung cancer risk and energy-adjusted quintiles[a] of dietary GL, GI, and GI (available carbohydrate) intake

	Quintiles of daily GI/GL					
	Q1	Q2	Q3	Q4	Q5	P_{trend}
Overall						
GL						
Cases/controls	358/483	332 (36.73)	409/477	353/479	430/488	
Minimally adjusted model[b]	1 (ref)	1.00 (0.82–1.22)	1.18 (0.97–1.44)	1.03 (0.84–1.26)	1.20 (0.98–1.45)	0.08
Fully adjusted model[c]	1 (ref)	1.04 (0.84–1.27)	1.12 (0.90–1.38)	1.04 (0.84–1.29)	1.16 (0.94–1.42)	0.19
GI						
Cases/controls	399/488	315/474	361/492	374/482	554/473	
Minimally adjusted model[b]	1 (ref)	1.08 (0.88–1.33)	1.14 (0.93–1.39)	1.11 (0.91–1.37)	1.59 (1.30–1.93)	<0.001
Fully adjusted model[c]	1 (ref)	1.11 (0.90–1.38)	1.16 (0.94–1.43)	1.16 (0.93–1.42)	1.49 (1.21–1.83)	<0.001
GI (available carbohydrate)						
Cases/controls	301/481	327/471	355/499	393/475	527/483	
Minimally adjusted model[b]	1 (ref)	1.08 (0.88–1.33)	1.09 (0.89–1.34)	1.20 (0.98–1.47)	1.49 (1.23–1.81)	<0.001
Fully adjusted model[c]	1 (ref)	1.18 (0.95–1.46)	1.11 (0.89–1.37)	1.30 (1.05–1.60)	1.48 (1.20–1.81)	0.001
By histologic subtype; adenocarcinoma						
GL						
Cases/controls	188/483	198/482	201/477	179/479	236/488	
Minimally adjusted model[b]	1 (ref)	1.05 (0.82–1.33)	1.08 (0.85–1.38)	0.97 (0.76–1.24)	1.22 (0.97–1.24)	0.2
Fully adjusted model[c]	1 (ref)	1.07 (0.83–1.38)	1.01 (0.79–1.30)	0.98 (0.76–1.27)	1.16 (0.91–1.47)	0.43
GI						
Cases/controls	179/488	189/474	177/492	184/482	273/473	
Minimally adjusted model[b]	1 (ref)	1.09 (0.86–1.39)	0.94 (0.74–1.20)	0.98 (0.76–1.25)	1.40 (1.11–1.77)	0.02
Fully adjusted model[c]	1 (ref)	1.13 (0.8–1.46)	0.98 (0.76–1.26)	1.01 (0.78–1.30)	1.30 (1.02–1.66)	0.1
GI (available carbohydrate)						
Cases/controls	176/481	196/471	170/499	204/475	256/483	
Minimally adjusted model[b]	1 (ref)	1.12 (0.88–1.42)	0.91 (0.71–1.17)	1.10 (0.87–1.17)	1.32 (1.05–1.67)	0.03
Fully adjusted model[c]	1 (ref)	1.23 (0.96–1.58)	0.93 (0.72–1.21)	1.15 (0.90–1.48)	1.31 (1.02–1.67)	0.08
By histologic subtype; SCC						
GL						
Cases/controls	84/483	69/482	97/477	75/479	90/488	
Minimally adjusted model[b]	1 (ref)	0.79 (0.55–1.13)	1.26 (0.90–1.77)	0.92 (0.64–1.31)	1.05 (0.75–1.49)	0.54
Fully adjusted model[c]	1 (ref)	0.82 (0.56–1.20)	1.28 (0.89–1.83)	0.97 (0.67–1.41)	1.05 (0.73–1.49)	0.65
GI						
Cases/controls	48/488	55/474	95/492	87/482	130/473	
Minimally adjusted model[b]	1 (ref)	1.14 (0.74–1.73)	1.79 (1.22–2.63)	1.57 (1.06–2.32)	2.08 (1.43–3.02)	<0.001
Fully adjusted model[c]	1 (ref)	1.07 (0.69–1.65)	1.68 (1.13–2.51)	1.56 (1.04–2.32)	1.92 (1.30–2.83)	<0.001
GI (available carbohydrate)						
Cases/controls	49/481	60/471	91/499	89/475	126/483	
Minimally adjusted model[b]	1 (ref)	1.13 (0.75–1.71)	1.61 (1.09–2.36)	1.63 (1.11–2.40)	1.94 (1.34–2.81)	<0.001
Fully adjusted model[c]	1 (ref)	1.14 (0.75–1.75)	1.56 (1.05–2.32)	1.73 (1.16–2.58)	1.92 (1.31–2.82)	<0.001

NOTE: Fully adjusted missing, $N = 55$; unknown physical activity, $N = 618$.

[a]Quintiles based on distribution in controls, by gender.

[b]Minimally adjusted model includes adjustment for age, education, gender, and smoking status; $N = 6$ missing education.

[c]Same as minimally adjusted, but also includes history of emphysema, pneumonia, hay fever, family history of lung cancer and physical activity, total energy intake, and BMI.

Table 3. Associations between lung cancer risk and energy-adjusted quintiles[a] of dietary GL, GI, and GI (total available carbohydrate) intake, stratified by smoking status and years of education

	Smoking status				Years of education			
	Never		Ever		<12		12+	
GL	Cases/controls	OR (95%CI)	Cases/controls	OR (95%CI)	Cases/controls	OR (95%CI)	Cases/controls	OR (95%CI)
Q1	39/101	1 (ref)	317/382	1 (ref)	128/114	1 (ref)	230/369	1 (ref)
Q2	52/111	1.28 (0.77–2.15)	293/365	0.97 (0.77–1.21)	133/122	1.05 (0.71–1.55)	220/360	1.05 (0.82–1.34)
Q3	62/122	1.39 (0.84–2.30)	329/351	1.06 (0.84–1.33)	174/124	1.30 (0.89–1.91)	235/353	1.07 (0.83–1.37)
Q4	70/134	1.40 (0.85–2.29)	280/343	0.96 (0.76–1.22)	159/114	1.38 (0.94–2.03)	194/365	0.91 (0.71–1.18)
Q5	85/122	1.81 (1.11–2.93)	343/362	1.01 (0.80–1.26)	198/129	1.55 (1.07–2.24)	232/359	1.03 (0.81–1.32)
P_{trend}		0.02		0.94		0.006		0.83
				$P_{interaction} = 0.04$				$P_{interaction} = 0.04$
GI								
Q1	49/131	1 (ref)	241/356	1 (ref)	85/93	1 (ref)	214/395	1 (ref)
Q2	64/120	1.40 (0.88–2.23)	250/352	1.01 (0.80–1.29)	96/103	1.04 (0.67–1.61)	219/371	1.13 (0.89–1.44)
Q3	61/127	1.34 (0.94–2.13)	299/362	1.10 (0.87–1.40)	123/125	1.11 (0.73–1.70)	238/367	1.19 (0.93–1.52)
Q4	57/117	1.41 (0.87–2.28)	315/359	1.09 (0.86–1.38)	196/124	1.77 (1.18–2.65)	178/358	0.93 (0.72–1.20)
Q5	77/95	2.25 (1.42–3.59)	457/374	1.31 (1.04–1.65)	292/158	1.75 (1.19–2.58)	262/315	1.37 (1.07–1.75)
P_{trend}		0.002		0.02		<0.001		0.11
				$P_{interaction} = 0.37$				$P_{interaction} = 0.02$
GI (available carbohydrate)								
Q1	47/127	1 (ref)	244/353	1 (ref)	95/94	1 (ref)	206/387	1 (ref)
Q2	55/124	1.21 (0.75–1.95)	271/345	1.16 (0.91–1.47)	101/116	0.99 (0.65–1.52)	226/355	1.25 (0.98–1.60)
Q3	65/119	1.56 (0.97–2.49)	288/372	1.01 (0.80–1.28)	130/116	1.14 (0.75–1.73)	225/383	1.09 (0.85–1.39)
Q4	63/111	1.68 (1.04–2.70)	329/363	1.20 (0.95–1.52)	189/120	1.71 (1.15–1.73)	204/355	1.14 (0.88–1.46)
Q5	78/109	2.06 (1.30–3.27)	430/370	1.36 (1.08–1.71)	277/157	1.77 (1.21–2.60)	250/326	1.33 (1.04–1.70)
P_{trend}		0.001		0.01		<0.001		0.09
				$P_{interaction} = 0.29$				$P_{interaction} = 0.01$

NOTE: Fully adjusted model where appropriate. Missing, $N = 55$.
[a]Quintiles based on distribution in controls, by gender.

High GL, GI, and GI_{ac} were significantly associated with lung cancer risk for individuals with less than 12 years of education (GL 5th vs. 1st quintile OR = 1.55; 95% CI, 1.07–2.24; P_{trend} 0.006; GI 5th vs. 1st quintile OR = 1.75; 95% CI, 1.19–2.58; P_{trend} <0.001; GI_{ac} 5th vs. 1st quintile OR = 1.77; 95% CI, 1.21–2.60; P_{trend} <0.001; Table 3). High GI and GI_{ac} were also associated with lung cancer risk in individuals with more than 12 years of education, but the effect estimates were attenuated and the trends were no longer significant. We observed interactions between GL ($P_{interaction} = 0.04$), GI ($P_{interaction} = 0.02$), and GI_{ac} ($P_{interaction} = 0.01$) and years of education on lung cancer risk. The remaining stratified analyses were consistent with the overall findings (not shown), with increased risk consistently associated with the highest quintile of GI across all subgroups; GI 5th versus 1st quintile; female = 1.43; 95% CI, 0.82–1.51; $P_{trend} = 0.01$; GI 5th versus 1st quintile; male = 1.40; 95% CI, 1.05–1.88; $P_{trend} = 0.05$; GI 5th versus 1st quintile; overweight/obese = 1.53; 95% CI, 0.84–1.99; $P_{trend} = 0.002$; GI 5th versus 1st quintile; normal weight = 1.67, 95% CI, 1.20–2.33, P_{trend} <0.001; GI 5th versus 1st quintile; age <60 = 1.37; 95% CI, 1.00–1.87; $P_{trend} = 0.04$; GI 5th versus 1st quintile; Age 60+ = 1.41; 95% CI, 1.07–1.86; $P_{trend} = 0.01$. Results for GI_{ac} are consistent with these findings and therefore not shown here.

Discussion

This is only the second study to suggest an independent association between GI and lung cancer risk and the first study to suggest that GI may influence lung cancer risk more profoundly in specific subgroups, including never smokers, individuals with low levels of education (<12 years), and those diagnosed with certain histologic subtypes of lung cancer, specifically SCC. In this case–control study, we observed a 49% increased risk of lung cancer associated with daily GI with consistent findings for GI_{ac}. Results for the two major histologic subtypes were consistent; however, more pronounced effects were observed between GI and SCC and between GL/GI and lung cancer risk in never smokers. In addition, we observed significant interactions between high GL, GI, and GI_{ac} and education.

A previous case–control study of 463 cases and 465 controls conducted in Uruguay found that GI and sucrose-to-dietary fiber ratio were significantly associated with lung cancer risk (OR = 2.77; 95% CI, 1.28–5.97 and OR = 1.77; 95% CI, 1.11–2.83, respectively; ref. 27). Although the associations between GI and GL have not been extensively studied with regards to lung cancer risk, previous studies of the association between these factors and other cancers have suggested a role for increased dietary GI and GL in cancer etiology.

Diets high in GI result in higher levels of blood glucose and insulin, which promote glucose intolerance, insulin resistance, and hyperinsulinemia (5, 6, 8). Insulin resistance is a pathologic condition, and previous studies suggest that insulin resistance is associated with abnormally high levels of growth factors, adipokines, reactive oxygen species, adhesion factors, and proinflammatory cytokines, all of which have been associated with neoplastic tissue survival and cancer stem cell development (34–36). Circulating levels of insulin have also been associated with a variety of different cancers (37) and may modulate cancer risk via perturbations in the IGF axis.

The IGF system is an integral part of growth regulation by the body and abnormalities in all levels of the IGF system have been implicated in carcinogenesis and cellular transformation (38, 39). IGFs, such as IGF-1, play a pivotal role in regulating cell proliferation, differentiation, and apoptosis. IGF-binding proteins normally inhibit the action of IGFs by blocking the binding of IGFs to their receptor (10). Lower levels of these binding proteins have

also been associated with increased cancer risk (40). In a previous case–control study of 204 histologically confirmed primary lung cancer patients and 218 control subjects, higher plasma levels of IGF-I and lower levels of IGFBP-3, an IGF-binding protein, were associated with an increased risk of lung cancer that persisted after adjustment for age, gender, BMI, smoking status, race, and family history of any cancer (10). This study also showed a significant dose–response relationship between levels of plasma IGF-1 and lung cancer risk. Results from animal experiments and cell cultures studies also suggest that IGF-1 is a potent mitogen for a variety of cancer cells including breast, prostate, lung, colon, and liver cells (41). The evidence for the association between the IGF system and lung cancer is inconsistent, however, with several studies suggesting a null association (42, 43). Further research is necessary to understand the underlying mechanisms linking GI/load, the insulin-like growth factor axis, and lung cancer risk in human populations.

The stratified analyses by smoking status showed a more profound, independent association between dietary GI and lung cancer risk in individuals without traditional lung cancer risk factors (i.e., smoking). Smoking is the most important risk factor for most lung cancers, therefore, it stands to reason that among smokers, GI might not play an overwhelming role in lung cancer risk. We did find, however, that smokers with high dietary GI had slightly larger effect estimates compared with smokers with low GI in the joint effects analysis (Fig. 1). Stratified analyses by other factors, such as years of education and histologic subtype, suggest possible joint or modifying effects between these risk factors and GI. Educational attainment is a proxy for socioeconomic status which has been linked with poor diet quality (including high intake of simple sugars and reduced intake of fiber) in various studies (44–46). Socioeconomic status is also closely linked with smoking behavior (47), therefore the associations between GI and lung cancer risk in individuals with less than 12 years of formal education may represent the joint impact of low diet quality and smoking on lung cancer risk.

SCC is the histologic subtype of lung cancer most closely linked with smoking behavior (48). Previous studies of dietary intake and lung cancer risk have suggested that the impact of dietary factors, such as fruit and vegetable intake, on lung cancer risk may be more pronounced in smokers and SCCs (49, 50). GI may have a more profound impact on SCC via IGF pathways. Smoking has been associated with expression of IGF-1 and IGF type 1 receptor (IGF-1R), particularly in SCCs of the lung (51–53). In our study,

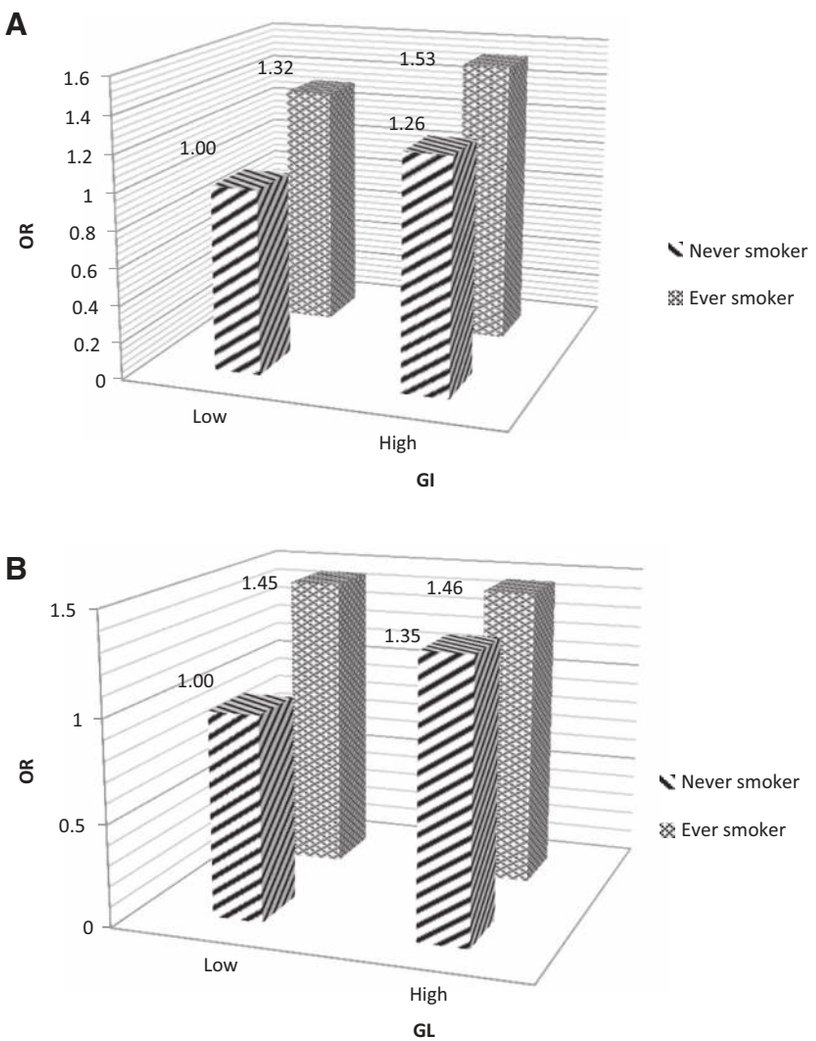

Figure 1.
Joint effect of GI (A) and GL (B) with smoking status in lung cancer risk (*P* values for all ORs are significant). Low and high are defined by the median cutoff in control. Fully adjusted model where appropriate, missing $N = 55$.

smokers and nonsmokers differed by various characteristics (see Supplementary Table S4) including histologic subtype and education; 95% of SCC cases were smokers and nearly 50% had less than 12 years of education compared with the 75% of ACs that were smokers and only 35% had less than 12 years of education. These differences are consistent with the existing literature and could account for the differential associations between GI and lung cancer risk in various subgroups (54–56). Future research is necessary to elucidate the mechanisms underlying the interplay between socioeconomic status, smoking behavior, GI, and lung cancer risk.

The current study has several strengths. It is the largest study of GL/GI and lung cancer risk to date and the first to be conducted in a U.S. population. We utilized a large sample size of newly diagnosed, histologically confirmed lung cancer cases and included detailed data on many potential risk factors, including dietary information from a validated FFQ. Finally, we conducted a thorough analysis (overall, stratified, and joint) matched on smoking status to address potential residual confounding by smoking status and other factors.

Although this study provides the first quantitative assessment of the association between GI and risk of lung cancer in a U.S. population, there are several limitations that should be addressed. It is a retrospective case–control study, meaning recall and reporting bias and confounding are important considerations. It is possible that cases report their dietary intake differently from healthy controls. For example, healthy controls are more likely to recall healthy dietary habits than patients, leading to biased effect estimates. However, it is unlikely that cases versus controls differentially reported dietary consumption based on GI values. Prospective cohort studies are required for estimating the causal association between diet and lung cancer. Smoking has been established as a cause of type II diabetes (57), and recent studies suggest an association between diabetes, diabetic medication (such as metformin), and lung cancer risk (58–61). Information regarding diabetes, hypertension, and heart disease were not collected within the scope of the current study until recently, and we do not currently have information regarding diabetic medication. Given the link between high GI diets (via insulin) and diabetes, this association warrants further attention in future studies. In addition, FFQs are subject to random and systematic error and are therefore not believed to accurately measure individual dietary intake, but rather, rank individuals well based on their relative intake. It is also possible that the association between GI and lung cancer varies by race and that the results of the current study, limited to non-Hispanic whites, are not generalizable to other ethnic or racial subgroups. This study provides additional evidence that diet may, independently and jointly with other risk factors, impact lung cancer etiology. Further research is necessary to understand the exact underlying mechanism for the association between dietary GI and lung cancer risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C.R. Daniel, X. Wu
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): X. Wu
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.C. Melkonian, C.R. Daniel, Y. Ye, X. Wu
Writing, review, and/or revision of the manuscript: S.C. Melkonian, C.R. Daniel, Y. Ye, J.A. Pierzynski, J.A. Roth, X. Wu
Study supervision: X. Wu

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