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Original Contribution

Dietary Boron and Hormone Replacement Therapy as Risk Factors for Lung Cancer in Women

S. Mahabir, M. R. Spitz, S. L. Barrera, Y. Q. Dong, C. Eastham, and M. R. Forman

From the Department of Epidemiology, University of Texas M. D. Anderson Cancer Center, Houston, TX.

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Hormone replacement therapy (HRT) may reduce lung cancer risk. Dietary boron may have actions similar to those of HRT; however, no previous study has reported the associations between dietary boron intake and lung cancer risk or the joint effects of boron intake and HRT use on lung cancer risk. The authors examined the associations between boron intake and the joint effects of boron intake and HRT on lung cancer risk in women. In an ongoing case-control study in Houston, Texas (July 1995 through April 2005, end date for this analysis), 763 women were diagnosed with lung cancer, and 838 were matched healthy controls with data on both diet and HRT. Multiple logistic regression analyses were conducted to assess the associations between dietary boron and HRT with lung cancer risk. After adjustment for potential confounders, the odds ratios for lung cancer with decreasing quartiles of dietary boron intake were 1.0, 1.39 (95% confidence interval (CI): 1.02, 1.90), 1.64 (95% CI: 1.20, 2.24), and 1.95 (95% CI: 1.42, 2.68) mg/day, respectively, for all women ($p_{trend} < 0.0001$). In joint-effects analyses, compared with women with high dietary boron intake who used HRT, the odds ratio for lung cancer for low dietary boron intake and no HRT use was 2.07 (95% CI: 1.53, 2.81). Boron intake was inversely associated with lung cancer in women, whereas women who consumed low boron and did not use HRT were at substantial increased odds.

boron; diet; hormone replacement therapy; lung neoplasms; risk factors; women

Abbreviations: CI: confidence interval; HHHQ, Health Habits and History Questionnaire; HRT, hormone replacement therapy.

Lung cancer incidence and mortality rates are higher in men than women in the United States (1). Cigarette smoking is the major exposure associated with lung cancer, but other factors such as diet and genetics may also contribute to causation. For example, evidence based on five prospective cohort studies demonstrated that lung cancer incidence is higher among women than men who have never smoked (2). We and others have previously suggested a protective role of hormone replacement therapy (HRT) (3, 4). In addition, association studies have examined the intakes of fruits and vegetables (5), certain micronutrients (6), macronutrients (7), phytochemicals (8), and essential trace metals (9) in lung cancer risk or prevention.

However, there is no published report on the role of dietary boron and lung cancer risk. Boron is a trace metal that is ubiquitous in foods commonly consumed in the United States, such as fruits, vegetables, nuts, legumes, wine, coffee, milk, and other beverages. There is no established recommended dietary intake for boron, because it is not established as an essential trace metal. However, emerging evidence suggests that optimal boron levels enhance several functions throughout the life cycle (10, 11). The mechanisms by which boron may affect lung cancer are not clear, but evidence exists that boron may have antioxidant and antiinflammatory properties (10–13). Reports have also indicated that levels of 17β-estradiol increase with dietary boron supplementation in human subjects (11, 14, 15). Therefore, an interesting possibility is that dietary boron may mimic the actions of hormone replacement therapy (16) to compensate for the decrease in endogenous estrogen

Correspondence to Dr. Somdat Mahabir, Department of Epidemiology-Unit 1340, University of Texas M. D. Anderson Cancer Center, CPB4.3241, 1155 Pressler Boulevard, Houston, TX 77030 (e-mail: smahabir@mdanderson.org).

levels following menopause. Because of the potential importance of dietary boron in host defense against cancer initiation due to inflammation and on the basis of our previous finding that HRT reduces lung cancer risk (3), we hypothesize that increased dietary intake of boron is protective against lung cancer. We further hypothesize that women who jointly have high intake of boron and use HRT are at a lower risk for lung cancer compared with women who have low boron intake and do not use HRT.

MATERIALS AND METHODS

Study population

Our study population of women included 763 newly diagnosed lung cancer patients (cases) and 838 healthy controls. The participants were a subset of a larger ongoing and previously described lung cancer case-control study (17). Briefly, lung cancer patients have been recruited from the Thoracic Center at the University of Texas M. D. Anderson Cancer Center since July 1995. The cases were all newly diagnosed patients presenting with histologically confirmed lung cancer and were enrolled prior to initiation of chemo- or radiation therapy. There were no age, ethnic, or stage restrictions. Considering that the lung cancer patients were of different stages, we also conducted stratified analysis by early and late-stage lung cancers. Healthy controls without a previous diagnosis of cancer were recruited from the Kelsey-Seybold clinics, the largest private multispecialty physician group of 23 clinics in the Houston, Texas, area. All participants were US residents. Controls were frequency matched to the cases by age within 5 years, ethnicity, and smoking status (current, former, and never) (18). Through April 2005 (end date for this analysis), response rates among both case patients and control subjects were approximately 75 percent. This research was approved by the M. D. Anderson Cancer Center and Kelsey-Seybold institutional review boards.

Epidemiologic and dietary data

Participants were interviewed in person to obtain demographic data, information on HRT use, and smoking history. Women were asked whether they had taken HRT in the previous 6 months—''yes'' or ''no.'' Those who answered ''yes'' were treated in the analysis as ''HRT users'' versus ''non-HRT users.'' Smokers of at least 100 cigarettes in their lifetimes were classified as ever smokers, among whom former smokers had quit smoking at least 1 year before diagnosis (cases) or before interview (controls). Race/ethnicity information was self-reported. Body mass index was estimated from self-reported weight prior to diagnosis in patients and height (weight (kg)/height $(m)^2$).

Dietary data were collected by trained interviewers using a modified version of the 135-item National Cancer Institute Health Habits and History Questionnaire (HHHQ). The HHHQ includes a semiquantitative food frequency list, an open-ended food section, and other dietary-behavior questions. Alcohol intake was also assessed as part of the HHHQ. The questionnaire has been shown to be valid and reliable across various populations (19, 20). Study participants were asked about their diet and alcohol intake during the year prior to diagnosis (cases) and the year prior to study enrollment (controls). Subjects were given a one-page serving size guide, which features photographs of ¼ cup, ½ cup, 1 cup, and 2 cups on plates, and ½, 1, and 2 cups in bowls (1 cup = 237 ml; Block Dietary Data Systems, Berkeley, California). Each line item of our food frequency questionnaire also included four quantitative serving size choices for that line item; for example, for corn, we ask, ''How many cups?'' and give four possible answers (¼, ½, 1, 2 cups). Nutrient intake was calculated by use of the DIETSYS + Plus, version 5.9, dietary analysis program (Block Dietary Data Systems). The DIETSYS + Plus database for the present study was expanded to include dietary boron and phytoestrogen values in foods consumed in the United States. Detailed methods of the creation of the database (21), its limitations (21), and its applications to assess risk of prostate (22), testicular (23), and breast (24) cancers have previously been published.

Statistical analysis

Pearson's χ^2 test was calculated to assess differences between women patients (cases) and controls by ethnicity, smoking status, education, family history of cancer in first-degree relatives, dietary supplement use, HRT use, and alcohol use. The Student t test was calculated to test differences in mean age, years of smoking, cigarettes smoked per day, body mass index, boron intake, and intake of total energy between cases and controls. In this population, all individuals fell within the cutoff points for reasonable caloric intake (ranging from 600 to 3,500 kcal for women) (25).

Quartiles of dietary boron (both crude and energy adjusted) intakes were created on the basis of the distribution of intake in control subjects. Energy-adjusted boron quartiles were calculated by regressing dietary boron intake on total calories and obtaining the residuals by the method of Willett and Stampfer (26). The residual value for each observation was then added to the mean dietary boron value for our population. Multiple logistic regression analysis was performed to calculate odds ratios and 95 percent confidence intervals for associations between dietary boron and lung cancer, adjusting for age, ethnicity, education, body mass index, alcohol (continuous), total calories (excluding alcohol calories), years of smoking, number of cigarettes smoked per day, vitamin/mineral supplement use, and family history of cancer in first-degree relatives (model 1). These variables were included in the models on the basis of a priori knowledge of risk factors for lung cancer and, hence, as potential confounders of the association between dietary boron and lung cancer. Since there has been a report each on dietary phytoestrogens (27), dietary trace metals (zinc, copper, and selenium) (17), and dietary folate (28) and lung cancer risk from the current study, we paid very careful attention to addressing these nutrients as potential confounders in the current analysis. Therefore, in addition to our current model 1, we created a second model (model 2), which included all the variables in model 1 plus dietary phytoestrogens (beta-sitosterol, campesterol, and stigmasterol) and fruit and vegetable intake. The values for these

phytoestrogens were available from the latest version of the US Department of Agriculture National Nutrient Database for Standard Reference, Release 19. We also created a third model (model 3), with all the variables in model 2 plus dietary zinc, copper, and selenium. In each of the three models, all the nutrient values were energy adjusted by the residual method, because the nutrient residuals and total caloric intake by definition are uncorrelated (26, 29). Thus, when nutrient residuals were used in the model, the coefficient for total caloric intake pertains to the full effect of this variable (26, 29). Further, total calories were included, because food sources of boron such as nuts are energy rich; the advantage of this model is that the full effects of calories can be observed (30). The fourth quartile (highest intake) was the reference category. We tested for the trends in association by dietary intake and lung cancer using the Wald test based on the ordinal dietary value (25). Potential interactions between dietary boron and other risk factors for lung cancer were tested on the multiplicative scale by entering the cross-product terms in the main-effects multivariate models. We also conducted subgroup analyses defined by age, body mass index (kg/m^2), smoking status (current, former, and never smokers), alcohol (nondrinkers and drinkers), years of smoking, number of cigarettes smoked per day, vitamin/mineral supplement use (yes and no), HRT use (yes and no), history of cancer in first-degree relatives, and lung cancer stage (early and late). We stratified age of the women at the median of the controls ($\leq$60 or $>$60 years). We could not stratify by $\leq$50 or $>$50 years, because very few younger women used HRT. Of the 272 women aged $\leq$50 years, only 53 (3 percent) reported using HRT. Body mass index was stratified as $\leq$25 or $>$25 because there were no underweight subjects, and the stratum of body mass index $>$25 includes both overweight and obese women. This cutoff was selected because a number of studies have reported that body mass index $>$25 is associated with protection against lung cancer (31–33). The variable years of smoking was stratified by the median-split ($\leq$31 or $>$31 years) in the controls. The variable cigarettes smoked per day was stratified to capture those who smoked $\leq$1 pack of cigarettes per day ($\leq$20 cigarettes) or $>$1 pack of cigarettes per day ($>$20 cigarettes). Early stage lung cancers were defined as cases with stage I and II non-small cell lung cancer and limited for small cell lung cancer. Late stage was defined as stages III and IV for non-small cell lung cancer and extensive for small cell lung cancer.

In joint-effects analyses for dietary boron and HRT, the reference group had those with high dietary boron (greater than the median-split for energy-adjusted boron intake in the controls) and users of HRT, because this group would be expected to have the lowest odds ratios. Low intake of dietary boron (less than or equal to the median-split) and nonusers of HRT would be expected to be at the highest odds for lung cancer. The top food sources for boron were calculated by the DIETSYS + Plus analysis program. Statistical analyses were performed with SAS, version 8.0, software (SAS Institute, Inc., Cary, North Carolina). All statistical tests were two sided, and a p value of less than 0.05 was considered statistically significant.

RESULTS

Population characteristics

The mean ages of the 763 cases and 838 controls were 60.75 and 60.11 years ($p = 0.24$) (table 1). More cases than controls reported less than a high school education, and conversely more controls reported attending college and graduate school. Cases compared with controls had fewer never and former smokers but more current smokers and reported a longer duration of smoking; current smokers reported a significantly ($p < 0.01$) higher number of cigarettes smoked per day. Cases had lower body mass index than did controls. More controls than cases reported taking HRT and had higher (crude and energy adjusted) boron intake. There were no significant differences in total caloric intake or alcohol intake, vitamin/mineral supplement use, or family history of cancer in first-degree relatives among cases and controls (table 1).

Boron intake and risk

The model shown in table 2 is the same as model 1 described in Materials and Methods. With this model, decreased boron intake was associated with a monotonically increasing odds of lung cancer corresponding to a 39 percent, 64 percent, and 95 percent increase by decreasing quartile of intake ($p_{trend} < 0.0001$). In model 2 that adds dietary phytoestrogens (beta-sitosterol, campesterol, and stigmasterol) and fruit and vegetable intake to model 1, decreased boron intake was associated with 40 percent, 63 percent, and 99 percent increased odds by decreasing quartile of intake ($p_{trend} = 0.0006$). In model 3 that adds dietary phytoestrogens (beta-sitosterol, campesterol, and stigmasterol), fruit and vegetable intake, zinc, copper, and selenium to model 1, decreased intake of boron was associated with a 39 percent, 60 percent, and 92 percent increased odds by decreasing quartile of intake ($p_{trend} = 0.001$). Since the magnitude of odds ratios and the 95 percent confidence intervals remained similar to those of model 1 shown in table 2, we do not present data for these additional models. The interaction between dietary boron intake and HRT use was statistically significant ($p = 0.0005$).

When stratified by HRT, the subjects in the lowest quartile of boron intake among HRT users had an odds ratio of 2.45 (95 percent confidence interval (CI): 1.48, 4.04) versus 1.68 (95 percent CI: 1.11, 2.55) for no-HRT users. We also conducted subgroup analyses defined by age ($\leq$60 years and $>$60 years), body mass index ($\leq$25 and $>$25), smoking status (current, former, and never smokers), years of smoking, number of cigarettes smoked per day, alcohol use, vitamin/mineral supplement use, and family history of cancer in first-degree relatives. There were significant ($p < 0.05$) trends for an inverse diet-lung cancer association in both age strata. Younger subjects ($\leq$60 years) in the lowest quartile of dietary boron intake had an odds ratio of 2.38 (95 percent CI: 1.48, 3.82) compared with 1.64 (95 percent CI: 1.06, 2.56) in older subjects ($>$60 years). We observed a significant inverse trend ($p < 0.0001$) among subjects with a body mass index of $>$25 corresponding to a 31 percent, 77 percent, and 122 percent

TABLE 1. Characteristics of the women (cases and controls), Houston, Texas, 1995–2005

Variable	Cases ($N = 763$)		Controls ($N = 838$)		p value*
	No.	%	No.	%	
Ethnicity					
Caucasian	612	80.21	622	74.22	
Hispanic	37	4.85	53	6.32	
African American	114	14.94	163	19.45	0.02
Education					
Less than high school	132	17.30	70	8.35	
High school	212	27.79	184	21.96	
College	340	44.56	475	56.68	
Graduate school	79	10.35	109	13.01	<0.01
Supplement use					
Yes	533	69.86	593	70.76	
No	230	30.14	245	29.24	0.69
Smoking status					
Never	169	22.15	225	26.85	
Former	275	36.04	312	37.23	
Current	319	41.81	301	35.92	0.03
HRT† use					
Yes	298	39.06	394	47.02	
No	465	60.94	444	52.98	<0.01
Family history of cancer					
Yes	220	28.87	231	27.57	
No	519	68.11	573	68.38	
Don't know	23	3.02	34	4.06	0.48
	Mean (SD†)		Mean (SD)		
Age, years	60.75 (11.01)		60.11 (10.69)		0.24
Alcohol, g/day	5.83 (14.83)		5.96 (13.97)		0.86
Years smoked					
Former	30.95 (12.80)		26.81 (11.75)		<0.01
Current	39.08 (10.62)		36.03 (11.72)		<0.01
Cigarettes per day					
Former	22.84 (13.59)		24.24 (15.52)		0.24
Current	24.09 (11.47)		17.96 (10.03)		<0.01
Body mass index, kg/m^2	26.01 (5.77)		28.11 (6.05)		<0.01
Total calories, kcal/day	1,732.54 (504.94)		1,775.59 (518.89)		0.09
Boron, μg/day	875.78 (334.55)		976.90 (386.03)		<0.01
Boron, μg/day‡	955.33 (310.96)		1,044.23 (360.71)		<0.01

* From χ^2 test for categorical variables and t test for continuous variables.
† HRT, hormone replacement therapy; SD, standard deviation.
‡ Energy adjusted.

increased odds for the second, third, and fourth quartiles of dietary boron intake, respectively, but nonsignificant effects for thinner women with a body mass index of ≤25.

There was an inverse association between dietary boron intake among never, former, and current smokers, but a significant trend was restricted to never and current smokers. When stratified by years of smoking, reduced boron intake was associated with a similar magnitude of risk among those who smoked ≤31 years or >31 years. However, when stratified by number of cigarettes smoked per day, although there was a significant trend for increased odds with decreasing boron intake among those who smoked ≤1 pack (≤20

TABLE 2. Odds ratios for dietary boron intake among lung cancer cases and controls by selected variables, Houston, Texas, 1995–2005*

Variable	Dietary boron intake (μg/day) in the control population†				p_{trend}
	Quartile 1 (>1,247.69)	Quartile 2 (976.01–1,247.69)	Quartile 3 (777.87–976.00)	Quartile 4 (≤777.86)	
All women					
Cases (no.)	122	178	211	252	
Controls (no.)	210	209	210	209	
OR‡ (95% CI‡)	1.00	1.39 (1.02, 1.90)	1.64 (1.20, 2.24)	1.95 (1.42, 2.68)	<0.0001
HRT‡ use					
Yes					
Cases (no.)	46	86	87	79	
Controls (no.)	108	100	105	81	
OR (95% CI)	1.00	1.99 (1.24, 3.18)	1.99 (1.23, 3.21)	2.45 (1.48, 4.04)	0.001
No					
Cases (no.)	76	92	124	173	
Controls (no.)	102	109	105	128	
OR (95% CI)	1.00	1.08 (0.7, 1.65)	1.54 (1.01, 2.37)	1.68 (1.11, 2.55)	0.005
Age, years					
≤60					
Cases (no.)	48	86	97	128	
Controls (no.)	100	85	108	118	
OR (95% CI)	1.00	2.09 (1.28, 3.41)	1.85 (1.14, 3.01)	2.38 (1.48, 3.82)	0.002
>60					
Cases (no.)	74	92	114	124	
Controls (no.)	110	124	102	91	
OR (95% CI)	1.00	1.05 (0.69, 1.6)	1.46 (0.96, 2.23)	1.64 (1.06, 2.56)	0.01
Body mass index, kg/m^2					
≤25					
Cases (no.)	66	95	96	121	
Controls (no.)	78	68	63	66	
OR (95% CI)	1.00	1.66 (1.03, 2.68)	1.49 (0.91, 2.43)	1.56 (0.95, 2.54)	0.14
>25					
Cases (no.)	56	83	115	131	
Controls (no.)	132	141	147	143	
OR (95% CI)	1.00	1.31 (0.85, 2.02)	1.77 (1.17, 2.69)	2.22 (1.45, 3.39)	<0.0001
Smoking status					
Never					
Cases (no.)	25	46	49	49	
Controls (no.)	44	58	57	66	
OR (95% CI)	1.00	1.31 (0.73, 2.34)	1.89 (1.07, 3.32)	2.16 (1.26, 3.7)	0.002
Former					
Cases (no.)	60	71	73	71	
Controls (no.)	96	79	79	58	
OR (95% CI)	1.00	1.26 (0.78, 2.03)	1.23 (0.75, 2.01)	1.59 (0.94, 2.69)	0.11
Current					
Cases (no.)	37	61	89	132	
Controls (no.)	70	72	74	85	
OR (95% CI)	1.00	1.39 (0.7, 2.78)	1.68 (0.85, 3.35)	2.00 (0.96, 4.16)	0.05
Years smoking					
≤31					
Cases (no.)	70	100	103	116	
Controls (no.)	138	122	136	139	
OR (95% CI)	1.00	1.58 (1.05, 2.39)	1.55 (1.02, 2.34)	1.83 (1.2, 2.81)	0.01
>31					
Cases (no.)	52	78	108	136	
Controls (no.)	72	87	74	70	
OR (95% CI)	1.00	1.03 (0.63, 1.7)	1.6 (0.97, 2.64)	1.81(1.1, 2.98)	0.005

Table continues

TABLE 2. Continued

Variable	Dietary boron intake (μg/day) in the control population†				p_{trend}
	Quartile 1 (>1,247.69)	Quartile 2 (976.01–1,247.69)	Quartile 3 (777.87–976.00)	Quartile 4 (≤777.86)	
Cigarettes per day					
≤20					
Cases (no.)	91	124	155	165	
Controls (no.)	145	167	173	179	
OR (95% CI)	1.00	1.13 (0.79, 1.64)	1.37 (0.95, 1.97)	1.5 (1.03, 2.17)	0.02
>20					
Cases (no.)	31	54	56	87	
Controls (no.)	65	42	37	30	
OR (95% CI)	1.00	2.34 (1.23, 4.42)	2.43 (1.26, 4.69)	4.06 (2.07, 7.97)	<0.0001
Alcohol use					
Yes					
Cases (no.)	92	95	100	110	
Controls (no.)	160	128	106	97	
OR (95% CI)	1.00	1.29 (0.87, 1.91)	1.69 (1.12, 2.54)	1.72 (1.13, 2.62)	0.005
No					
Cases (no.)	30	83	111	142	
Controls (no.)	50	81	104	112	
OR (95% CI)	1.00	1.64 (0.92, 2.9)	1.67 (0.96, 2.9)	2.21 (1.27, 3.85)	0.008
Supplement use					
Yes					
Cases (no.)	93	142	149	149	
Controls (no.)	172	157	140	124	
OR (95% CI)	1.00	1.55 (1.09, 2.21)	1.71 (1.19, 2.46)	1.88 (1.3, 2.73)	0.0009
No					
Cases (no.)	29	36	62	103	
Controls (no.)	38	52	70	85	
OR (95% CI)	1.00	0.82 (0.4, 1.66)	1.26 (0.65, 2.44)	1.88 (0.98, 3.6)	0.008
History of cancer					
Yes					
Cases (no.)	39	52	65	64	
Controls (no.)	49	60	58	64	
OR (95% CI)	1.00	1.07 (0.59, 1.95)	1.19 (0.65, 2.19)	1.09 (0.59, 2.04)	0.70
No					
Cases (no.)	83	126	146	188	
Controls (no.)	161	149	152	145	
OR (95% CI)	1.00	1.51 (1.04, 2.18)	1.81 (1.25, 2.62)	2.34 (1.61, 3.4)	<0.0001
Clinical stage					
Early					
Cases (no.)	39	52	65	64	
Controls (no.)	49	60	58	64	
OR (95% CI)	1.00	1.07 (0.59, 1.95)	1.19 (0.65, 2.19)	1.09 (0.59, 2.04)	0.17
Late					
Cases (no.)	83	126	146	188	
Controls (no.)	161	149	152	145	
OR (95% CI)	1.00	1.51 (1.04, 2.18)	1.81 (1.25, 2.62)	2.34 (1.61, 3.4)	<0.0001

* All odds ratios adjusted for age, ethnicity, education, body mass index, alcohol (continuous), total calories (alcohol calories excluded), years smoking, number of cigarettes per day, supplement use, and family history of cancer (model 1).

† Energy adjusted.

‡ OR, odds ratio; CI, confidence interval; HRT, hormone replacement therapy.

cigarettes) or >1 pack (>20 cigarettes) per day, within the lowest quartile of boron intake, the highest odds increase was seen for the heavier smokers.

For both alcohol drinkers and nondrinkers, reduced dietary boron intake was associated with a similar magnitude of increased odds of lung cancer. Decreasing dietary boron intake

TABLE 3. Odds ratios for the joint effects of boron intake and hormone replacement therapy among lung cancer cases and controls, Houston, Texas, 1995–2005*

Variable	High intake† + HRT‡	High intake + no HRT	Low intake + HRT	Low intake + no HRT	*p* value
All women					
Cases (no.)	132	168	166	297	
Controls (no.)	208	211	186	233	
OR‡ (95% CI‡)	1.00	1.33 (0.98, 1.82)	1.37 (1.00, 1.88)	2.07 (1.53, 2.81)	<0.0001
Age, years					
≤60					
Cases (no.)	67	67	86	139	
Controls (no.)	99	86	94	132	
OR (95% CI)	1.00	1.44 (0.89, 2.34)	1.49 (0.94, 2.36)	1.84 (1.15, 2.94)	0.01
>60					
Cases (no.)	65	101	80	158	
Controls (no.)	109	125	92	101	
OR (95% CI)	1.00	1.33 (0.88, 2.02)	1.28 (0.82, 1.99)	2.32 (1.50, 3.60)	0.0003
Body mass index, kg/m^2					
≤25					
Cases (no.)	71	90	77	140	
Controls (no.)	84	62	68	61	
OR (95% CI)	1.00	1.72 (1.08, 2.74)	1.11 (0.69, 1.79)	2.00 (1.24, 3.23)	0.03
>25					
Cases (no.)	61	78	89	157	
Controls (no.)	124	149	118	172	
OR (95% CI)	1.00	1.11 (0.73, 1.69)	1.54 (1.00, 2.36)	1.99 (1.33, 2.98)	0.0001
Smoking status					
Never					
Cases (no.)	33	38	33	65	
Controls (no.)	47	55	40	83	
OR (95% CI)	1.00	1.06 (0.56, 2.00)	1.36 (0.69, 2.70)	1.60 (0.86, 2.98)	0.09
Former					
Cases (no.)	62	69	54	90	
Controls (no.)	91	84	68	69	
OR (95% CI)	1.00	1.24 (0.77, 2.00)	1.05 (0.63, 1.75)	1.69 (1.03, 2.77)	0.07
Current					
Cases (no.)	37	61	79	142	
Controls (no.)	70	72	78	81	
OR (95% CI)	1.00	1.76 (0.98, 3.14)	1.97 (1.12, 3.46)	2.93 (1.67, 5.12)	0.0002
Years smoking					
≤31					
Cases (no.)	72	98	73	146	
Controls (no.)	126	134	115	160	
OR (95% CI)	1.00	1.36 (0.91, 2.04)	1.16 (0.75, 1.79)	1.91 (1.27, 2.88)	0.005
>31					
Cases (no.)	60	70	93	151	
Controls (no.)	82	77	71	73	
OR (95% CI)	1.00	1.35 (0.82, 2.22)	1.66 (1.02, 2.70)	2.26 (1.39, 3.66)	0.0006

Table continues

was associated with a significant trend for increased odds among both users and nonusers of vitamin/mineral supplements. A significant trend ($p < 0.0001$) for increased odds with decreasing levels of dietary boron was observed only for subjects without a family history of cancer in first-degree relatives.

Joint-effects analysis: boron plus HRT

In a previous analysis using a smaller sample of women, we reported that HRT use was associated with lower odds for lung cancer (3). In the current analysis, HRT users versus nonusers had a 31 percent (odds ratio = 0.69, 95 percent

TABLE 3. Continued

Variable	High intake† + HRT	High intake + no HRT	Low intake + HRT	Low intake + no HRT	*p* value
Cigarettes per day					
≤20					
Cases (no.)	91	124	113	207	
Controls (no.)	147	165	158	194	
OR (95% CI)	1.00	1.30 (0.91, 1.86)	1.16 (0.80, 1.68)	1.92 (1.34, 2.74)	0.0007
>20					
Cases (no.)	41	44	53	90	
Controls (no.)	61	46	28	39	
OR (95% CI)	1.00	1.64 (0.88, 3.08)	2.60 (1.33, 5.07)	2.47 (1.33, 4.62)	0.002
Alcohol use					
Yes					
Cases (no.)	88	99	78	132	
Controls (no.)	148	140	100	103	
OR (95% CI)	1.00	1.24 (0.84, 1.82)	1.27 (0.83, 1.94)	2.14 (1.42, 3.24)	0.0005
No					
Cases (no.)	44	69	88	165	
Controls (no.)	60	71	86	130	
OR (95% CI)	1.00	1.39 (0.82, 2.37)	1.38 (0.83, 2.31)	1.87 (1.15, 3.04)	0.01
Supplement use					
Yes					
Cases (no.)	107	128	132	166	
Controls (no.)	175	154	131	133	
OR (95% CI)	1.00	1.47 (1.04, 2.07)	1.49 (1.04, 2.12)	1.93 (1.36, 2.75)	0.0005
No					
Cases (no.)	25	40	34	131	
Controls (no.)	33	57	55	100	
OR (95% CI)	1.00	0.95 (0.47, 1.91)	0.98 (0.48, 2.03)	2.17 (1.13, 4.15)	0.002
History of cancer					
Yes					
Cases (no.)	49	42	48	81	
Controls (no.)	55	54	58	64	
OR (95% CI)	1.00	0.88 (0.49, 1.58)	0.78 (0.43, 1.39)	1.35 (0.76, 2.39)	0.4
No					
Cases (no.)	83	126	118	216	
Controls (no.)	153	157	128	169	
OR (95% CI)	1.00	1.61 (1.12, 2.34)	1.75 (1.19, 2.57)	2.49 (1.72, 3.60)	<0.0001
Clinical stage					
Early					
Cases (no.)	43	40	35	81	
Controls (no.)	208	211	186	233	
OR (95% CI)	1.00	0.93 (0.57, 1.51)	0.82 (0.49, 1.38)	1.71 (1.08, 2.70)	0.02
Late					
Cases (no.)	70	101	97	164	
Controls (no.)	208	211	186	233	
OR (95% CI)	1.00	1.53 (1.06, 2.22)	1.59 (1.09, 2.33)	2.16 (1.50, 3.10)	<0.0001

* All odds ratios adjusted by age, ethnicity, education, body mass index, alcohol (continuous), total calories (alcohol calories excluded), years smoking, number of cigarettes per day, supplement use, and family history (model 1).

† High boron intake is defined as higher than the median split for energy-adjusted dietary boron intake in the control population; low dietary boron intake is defined as lower than the median split for energy-adjusted dietary boron intake in the control population.

‡ HRT, hormone replacement therapy; OR, odds ratio; CI, confidence interval.

CI: 0.56, 0.86) odds reduction for lung cancer after adjusting for potential confounders (data not shown).

In dietary boron-HRT joint-effects analysis, compared with subjects with high dietary boron who were HRT users

TABLE 4. Top 10 food sources of boron as reported by cases and controls, Houston, Texas, 1995–2005

Cases		Controls	
Food	%	Food	%
Coffee	9.9	Coffee	8.6
Wine	6.2	Wine	7.8
Apples and pears	4.8	Apples and pears	5.4
Peanuts and peanut butter	4.2	Peanuts and peanut butter	5.1
Orange juice	3.5	Grapes	4.9
Grapes	3.4	Salads	3.5
Salads	3.2	Orange juice	2.6
Bananas	2.5	Beans	2.5
Beans	2.4	Bananas	2.4
Broccoli	2.3	Broccoli	2.3

(referent group), there were 33 percent, 37 percent, and twofold increases in the odds of lung cancer for nonusers of HRT who had high dietary boron, low dietary boron and HRT use, and low dietary boron and nonuse of HRT, respectively (table 3) ($p_{trend} < 0.0001$).

There was a significant trend for increased odds in both age strata ($\leq$60 and >60 years) across the boron-HRT groups, and the highest risk (more than twofold) was observed in the low dietary boron plus HRT nonuser group who were older subjects. We also did stratified analysis by $\leq$50 and >50 years to represent pre- and postmenopausal years. Although too few women aged $\leq$50 years were in each of the four boron-HRT categories, once again the highest odds (odds ratio = 2.37, 95 percent CI: 1.68, 3.35) were observed in the low dietary boron-HRT nonusers aged >50 years (data not shown). In the two body mass index strata representing lean to normal weight and overweight to obesity (body mass index: $\leq$25 and >25), similar odds for lung cancer appeared in the low dietary boron-HRT nonuser group. For current smokers, there was a significant trend concomitant with 76 percent, 97 percent, and almost twofold increased odds for lung cancer, respectively, for the boron-HRT groups compared with the referent group. It was also evident that long-term (>31 years) and heavy (>20 cigarettes per day) smokers had the highest odds for lung cancer if they had low boron intake and did not use HRT. For alcohol drinkers, the odds were higher than for nondrinkers in the low dietary boron-HRT nonuser group, with an odds ratio of 2.14 versus 1.87.

The pattern was again evident for nonusers of supplements ($p_{trend} = 0.002$). These associations were also more pronounced for women with late-stage disease ($p_{trend} < 0.0001$).

We also evaluated the food contributors to boron intake in our population (table 4). Although it is obvious that boron is ubiquitous in the food supply, the top 10 sources include coffee, wine, apples and pears, peanut butter and peanuts, and grapes.

DISCUSSION

To our knowledge, this is the first study to have compared dietary boron intake among lung cancer cases and controls. The principal findings were that boron intake is inversely associated with the odds for lung cancer, whereas low boron intake jointly with no HRT use is associated with increased odds for this disease in women. To the extent possible, as explained in the Materials and Methods and Results sections, we have addressed the scientific validity of these findings, because our models addressed the role of other dietary factors as potential confounders. Thus, we believe that our data demonstrate the independent associations of dietary boron.

Few studies of dietary boron and cancer have been conducted, and those that have been conducted, including ours, are based on a boron database from published analytical values. On the basis of this approach, there is one report each of dietary boron and prostate cancer (34) and breast cancer (24) showing significant inverse associations.

Although the mechanisms by which dietary boron may protect against lung cancer are unknown, physiologically dietary boron may act like HRT by elevating estrogen levels because boron supplementation in healthy postmenopausal women and male subjects has been shown to elevate 17β-estradiol levels (11, 14, 15). We have previously reported (3) and have confirmed in this study that HRT use protects against lung cancer in women. We know that, in the female reproductive organs, estrogens initiate and promote tumor growth by interaction with estrogen receptors (35). Estrogen receptors are also present in both normal (36) and malignant (36, 37) lung tissue; however, the role of estrogens in lung cancer is unclear. A possible explanation for reduction in lung cancer risk may be that estrogen receptors also have the ability to bind various substrates other than estrogen (38), including carcinogenic polycyclic aromatic hydrocarbons from cigarette smoke condensate. Women with high dietary boron intakes, as well as HRT users, may exhibit hormone levels that may more readily bind to the estrogen receptors than the carcinogens from cigarette smoke. If this mechanism is correct, increasing boron intakes and HRT use may limit the carcinogenic potential from cigarette smoke as well as other carcinogens in lung tissues, which otherwise could become activated by cytochrome P450 enzymes. This might explain why the highest quartile of boron intake was associated with the lowest risk in current smokers, and why the highest risk was observed for current smokers who had low intakes of dietary boron but no HRT use. Other mechanisms by which dietary boron may affect lung cancer risk include its antioxidant and antiinflammatory properties (10–13). These functions of dietary boron are important in maintaining the integrity of the cell and in the prevention of lung and other cancers.

In general, our study found substantial increases in lung cancer risk among the women with low dietary boron intake but no HRT compared with high boron intake plus HRT use (table 3). In addition to the risks for current smokers, higher risks appeared among subjects who were older, had longer duration of smoking, had a greater number of cigarettes smoked per day, were alcohol drinkers, and were users of vitamin mineral supplements; among nonusers of vitamin

mineral supplements, increased risk was observed only in the low dietary boron intake plus no HRT group. Unfortunately, the dosage and frequency of vitamin mineral supplement use were unavailable for more detailed analysis.

This case-control study was originally designed to study genetic susceptibility to lung cancer, while the present data represent secondary analysis. Our data on HRT use are based on use in the past 6 months only. One could speculate that more detailed information on duration of use would have been more valuable. Future investigations of HRT and lung cancer should consider more detailed assessment of HRT use including describing HRT use such as current, former, and never users. Like all case-control studies, our analysis raises concern about recall bias and residual confounding. We recognize that our study would be strengthened by more objective measurements of boron status, such as serum or intracellular measurements; however, biologic samples are unavailable for boron measurements. In an attempt to reduce biased reporting of dietary intake in cases and controls, cases reported their diet during the year prior to diagnosis, and controls reported their diet during the year prior to enrollment into the study. The food frequency questionnaire is practical for large epidemiology studies such as ours, but its use may introduce measurement error (39, 40). In an effort to improve the accuracy, our interviewers were trained in food frequency questionnaire administration, while questionnaire responses were reviewed and requeried by staff nutritionists. Portion sizes (for meat only) were assessed with visual aids. It is well recognized that the food frequency questionnaire can reliably classify individuals by quartile of intake (41). There is no national boron nutrient database maintained by the US Department of Agriculture. Therefore, errors could arise from the source of dietary boron values in the food composition database that was developed (21). As stated in Materials and Methods, the values for boron were derived from analytical values available in the literature for foods consumed in the United States, but these values may not represent an adequate variety of foods by regions or grown under different conditions that may have different levels of boron. Although recall bias may exist in our study, the mean caloric intake did not differ between cases and controls. Further, our control population consumed daily mean dietary boron intakes comparable to values reported by Rainey et al. (42), who authored the largest study to date of daily boron intake from the American diet. Their study (42) had a boron database created from analytical values in the literature that were linked to 3-day food records of 11,009 respondents to the 1989–1991 Continuing Survey of Food Intakes by Individuals (CSFII) to generate average daily boron intake. The mean boron intake for the control women in our study was 0.98 (standard deviation: 0.39) mg/day, whereas the mean boron intake for women in the study by Rainey et al. (42) was 0.96 (standard deviation: 0.55) mg/day.

Among the food contributors to boron intake (table 4), no single food was a major contributor of boron content of the diet, since it is ubiquitous in the diet. Although the DIETSYS + Plus database constitutes a wide cross-section of foods, we did not have data to compare the boron composition of foods in the Houston area, where most of our participants resided.

The role of dietary trace metals in lung cancer remains an understudied area of research. Our findings suggest that boron from food sources in the typical US diet, with or without HRT use, offers protection against lung cancer in women. More research on the role of dietary boron and lung carcinogenesis is warranted.

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