Calcium intake and lung cancer risk among female non-smokers: A report from the Shanghai Women's Health Study

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Abstract

Background—Calcium has been implicated in carcinogenesis and linked to the risk of several cancers in epidemiologic studies; however, few studies have investigated the association of calcium intake with lung cancer risk, particularly among non-smokers.

Methods—We evaluated the association of intakes of calcium and related minerals, assessed through a food frequency questionnaire, with lung cancer risk among 71,267 female non-smokers who were cancer free at baseline in the Shanghai Women's Health Study, a population-based, prospective cohort study. Multivariate Cox regression was used to calculate hazard ratios (HR) and 95% confidence intervals (CI).

Results—During follow-up through December 2009 (median follow-up time: 11.2 years), 428 incident lung cancer cases accrued. The median intakes of dietary calcium, magnesium, and phosphorus were 441, 266, and 935 mg/day, respectively. Intakes of calcium, phosphorus, and the calcium-to-magnesium (Ca:Mg) ratio were inversely associated with lung cancer risk. The corresponding HRs (95% CIs) for the highest compared with the lowest quartile were 0.66 (0.48, 0.91) for calcium, 0.55 (0.36, 0.85) for phosphorus, and 0.62 (0.47, 0.82) for the Ca:Mg ratio. No association was observed for dietary magnesium intake or the use of calcium- or vitamin D-containing supplements.

Conclusions and Impact—Our study provides some of the first evidence suggesting a possible role for increasing dietary calcium intake in lung cancer prevention among female non-smokers, especially in populations with relatively low calcium intake.

Keywords

calcium; dietary intake; lung cancer; women; non-smokers

Introduction

Evidence from *in vitro* and experimental studies suggests a potential role of calcium and vitamin D in carcinogenesis, especially through cell signaling and cell cycle regulation (1). Calcium intake, either from foods and supplements, has been linked to the risk of several cancers including colorectal, breast, and prostate cancers, in previous epidemiologic studies (2-6). To date, few studies have investigated the association between dietary calcium intake

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and lung cancer risk with mixed results. Two studies observed no overall association (7, 8), and another reported a significant positive association (9). Vitamin D, in the active form 1,25-dihydroxyvitamin D, promotes calcium absorption and, together with calcium, can affect carcinogenesis through various mechanisms (1). Similar to calcium, inconsistent results have been reported for the association between circulating 25-hydroxyvitamin D level and lung cancer. Overall, there have been null findings in three studies (10-12), an inverse association among women in one study (11), and a positive association among men in another (10). Other minerals affecting calcium absorption and vitamin D metabolism, such as magnesium and phosphorus, were also examined in a few studies of lung cancer (7-9). The ratio of calcium to magnesium has been used to indicate calcium absorption and was examined in a previous study of colorectal cancer (13); however, to our knowledge, the calcium-to-magnesium (Ca:Mg) ratio has not been investigated with respect to lung cancer risk.

Unlike many North American and European countries, where the majority of previous studies have been conducted, the consumption of dairy foods in China is relatively uncommon (43.3% reported no intake of dairy foods in our study) and a considerable amount of calcium intake comes from non-dairy foods such as rice and vegetables. As a result, calcium intake in our study population is lower than that in North American and European populations (7-9). In addition, foods are rarely fortified with vitamin D in China and the prevalence of vitamin D deficiency in our population is relatively high (56% based on the cut-off of <37.5 nmol/L used to determine vitamin D deficiency in the United States) (14). Despite a very low prevalence of smoking among women in China (2.4%) (15), lung cancer incidence is higher there than in other populations of women with low smoking prevalence (e.g., 19.0 per 100,000 person-years in China vs. 12.3 per 100,000 person-years in Japan) (16). In addition, risk factors for lung cancer among non-smokers are not well understood (17). Hence, the unique dietary and nutrient intake patterns, low smoking prevalence, and high lung cancer incidence among Chinese women provides a unique opportunity to evaluate associations between calcium intake and lung cancer risk among female non-smokers.

Materials and Methods

Study population

The current analysis is based on the Shanghai Women's Health Study, a population-based, prospective cohort study of 74,941 Chinese women who were aged 40 to 70 years and were permanent residents of urban areas of Shanghai at the time of study recruitment (18). The recruitment occurred between March 1997 and May 2000 through in-person interviews with an overall response rate of 92.7%. Interviewers administered questionnaires at the baseline and follow-up visits that collected information on demographics, medical history, lifestyle (e.g., smoking, drinking, and exercise), reproductive history, occupation history, family history of cancer, and dietary habits. Body weight, height, and waist and hip circumferences were measured by trained interviewers during the baseline visit. Information on passive smoking was collected during the first follow-up visit. Informed consent was provided by all participants, and the study protocol was approved by the Institutional Review Board of all participating research institutions.

Dietary intake and supplement use assessment

The participants completed an interviewer-administered food frequency questionnaire (FFQ) during home visits. The FFQ was validated against 24 monthly 24-hour dietary recalls among 200 SWHS participants (19). The Spearman correlation coefficients between self-reported intakes from the FFQ and these multiple 24-hour dietary recalls were 0.50 for

calcium, 0.51 for magnesium, and 0.52 for phosphorus. Total caloric and nutrient intakes were calculated based on the values listed in the Chinese Food Composition Tables (20). Dairy food intake was calculated as the sum of fresh milk intake and the liquid equivalent of fresh milk intake based on milk powder intake. Use of supplements containing calcium or vitamin D and the use of multivitamin supplements were assessed at baseline and the first follow-up, while the use of vitamin A/D supplements and calcium tablets were assessed only at the first follow-up.

Cancer ascertainment and follow-up

The cohort was followed by in-person surveys every two to three years supplemented by annual record linkage to the Shanghai Cancer Registry and Vital Statistics Registry databases. The response rates for the first, second, third, and fourth in-person follow-up surveys were 99.8%, 98.7%, 96.7%, and 92.0%, respectively. Cases ascertained through in-person surveys and database linkages were verified by home visits and by medical chart review. Information on histologic types of lung cancer was extracted from medical charts. The current analysis includes 428 lung cancer cases who were diagnosed between April 1998 and December 2009.

Statistical analysis

In the current analysis, 1,579 participants were excluded due to prior history of cancer at baseline, 2,042 were excluded due to a history of smoking, 45 were excluded since they reported total caloric intake outside the range of 500 to 4,000 Kcal per day, and eight were excluded due to no follow-up data. A total of 71,267 participants were included in the current analyses. Baseline characteristics of the study population were compared between cases and the rest of the cohort (non-cases) after adjusting for age at baseline. Comparisons of nutrient and dairy food intakes at baseline were made between the two groups after further adjusting for total caloric intake. Spearman correlation coefficients were calculated between intakes of minerals and food groups.

Quartiles of intake were created based on the distribution of baseline intakes among all participants. The median value of each quartile was assigned to test for linear trend. Cox proportional hazards regression was performed to estimate the hazard ratios (HR) and the corresponding 95% confidence intervals (CI) for the risk of lung cancer associated with increasing intakes of calcium and related minerals or with intake of any dairy food and the use of calcium- or vitamin D-containing supplements. Covariates included in the analysis were age at baseline (continuous), total caloric intake (continuous), income (four categories), occupation (four categories), passive smoking status (none, at home, in the workplace, or both), history of asthma (binary), and body mass index (BMI, five categories), which were selected due to significant associations with lung cancer risk or known associations with lung cancer or dietary intakes. Since sunlight exposure was not directly assessed in our study, we used minutes reported for walking and/or biking related to commuting or other purposes and total time spent outdoors for leisure activities as a surrogate for sunlight exposure, because these activities are the main outdoor activities in our study population.

Stratified analyses for associations with dietary calcium intake were conducted for passive smoking status, menopausal status (postmenopausal status was defined as cessation of natural menstruation for 12 months or longer that was not due to breastfeeding), and time spent outdoors in leisure-time activities (none, low, or high). We assessed joint effects of dietary calcium intake (quartiles) with: 1) calcium-containing supplement use (yes or no); 2) vitamin D-containing supplement use (yes or no); and 3) calcium- and/or vitamin D-containing supplement use (neither or either/both) on lung cancer risk with women in the

lowest quartile of dietary intake and who had no use of the respective supplement as the reference. Potential interactions of dietary calcium intake with the use of calcium- and/or vitamin D-containing supplements were evaluated by including cross-product terms in the model and assessing the *P*-value. The risk of a specific histologic type, adenocarcinoma, was also investigated separately. All statistical analyses were conducted by using SAS 9.3 package (Cary, NC). All *P*-values were two-sided.

Results

A total of 428 lung cancer cases were documented during a median follow-up of 11.2 years. Cases were about 7 years older than non-cases (**Table 1**). There were 186 cases with adenocarcinoma, 13 cases with squamous cell carcinoma, 19 cases with adenosquamous carcinoma, 27 cases with the other subtypes, and 183 cases with missing information for cancer subtype. Socioeconomic status, measured by education, income and occupation, and lifestyle factors, including regular alcohol and tea consumption and regular exercise, were similar between cases and non-cases. Family history of any cancer or lung cancer did not differ between the two groups nor did passive smoking status, menopausal status, BMI, or waist-to-hip ratio. Among participants with a history of lung disease, slightly more cases reported having had asthma than non-cases, while the proportions for tuberculosis and chronic bronchitis were similar.

The median intakes of dietary calcium, magnesium, and phosphorus at baseline were 441, 266, and 935 mg/day, respectively. Total caloric intake was similar between cases and non-cases (**Table 2**). Total fat intake was slightly higher in cases than non-cases, while carbohydrate intake was lower in cases than non-cases. Cases had lower intake of dietary calcium than non-cases. The Ca:Mg ratio was lower among cases than non-cases. The Spearman correlation coefficients between calcium intake and intakes of phosphorus (r = 0.82, P <.0001) and magnesium (r = 0.73, *P*<.0001) were relatively high, after adjusting for total caloric intake (data not shown). Among the food groups, the highest correlation of calcium intake was observed with rice (r = -0.62, *P*<.0001), followed by dairy foods (r = 0.61, *P*<.0001), and total vegetable intake (r = 0.53, *P*<.0001). Major food sources of calcium intake were soy foods (27.1% of total calcium intake), total vegetables (26.6%), and dairy foods (16.8%).

Dietary intakes of calcium and phosphorus were inversely associated with lung cancer risk; those in the highest quartile had 34% and 45% lower risk, respectively, than those in the lowest quartile (HR = 0.66; 95% CI: 0.48, 0.91; *P* for trend = 0.007 for calcium intake and HR = 0.55; 95% CI: 0.36, 0.85; *P* for trend = 0.02 for phosphorus intake) (**Table 3**). There was no association for magnesium intake. The Ca:Mg ratio was inversely associated with the risk of lung cancer (HR = 0.62; 95% CI: 0.47, 0.82; *P* for trend = 0.003). When calcium and other mineral intakes were entered into the model simultaneously, the inverse association for calcium intake was strengthened after adjustment for magnesium intake (HR = 0.56; 95% CI: 0.37, 0.83; *P* for trend = 0.003). When further adjusted for phosphorus intake, the inverse association for the Ca:Mg ratio was slightly attenuated (HR = 0.67; 95% CI: 0.49, 0.92; *P* for trend = 0.04).

Use of calcium- or vitamin D-containing supplements was not significantly associated with the risk of lung cancer (HR = 0.89; 95% CI: 0.72, 1.10 for calcium and HR = 1.11; 95% CI: 0.87, 1.41 for vitamin D) (**Table 4**). Women who consumed any amount of dairy food had a 21% lower risk than those who did not (HR =0.79; 95% CI: 0.65, 0.96). Soy food intake was inversely associated with lung cancer risk in our study population, as we reported in a separate publication (21), although total vegetable intake was not (HR= 0.93; 95% CI: 0.70, 1.23). Further adjustment for soy food intake did not materially change the significant

inverse association for calcium intake (HR = 0.66; 95% CI: 0.46, 0.95; *P* for trend = 0.02) or for the Ca:Mg ratio (HR = 0.63; 95% CI: 0.47, 0.84; *P* for trend = 0.01). Neither did adjustment for total vegetable intake change the association (HR = 0.60; 95% CI: 0.42, 0.88; *P* for trend = 0.0005). However, adjustment for dairy food intake attenuated, but did not eliminate the association (HR = 0.73; 95% CI: 0.51, 1.04). There was no association between time spent in outdoor activities and risk of lung cancer; the HR (95% CI) for those in the highest quartile of duration of total walking and biking activities (median: 5 hours per day) compared with those in the lowest quartile (median: 1 hour per day) was 1.11 (0.84, 1.46).

In joint analyses, regardless of the use of calcium- and/or vitamin D-containing supplements, dietary calcium intake was inversely associated with lung cancer risk (**Table 5**), although point estimates were not significant in all strata due to small sample sizes. Tests for multiplicative interaction were not significant (*P* for interaction = 0.28-0.69). When stratified by passive smoking status, the inverse association remained statistically significant and was slightly stronger among women who had no passive smoking than among those who had passive smoking exposure at home or in the workplace (**Supplementary Table 1**). However, the test for multiplicative interaction effect was not statistically significant (*P* for interaction = 0.87). In analyses stratified by menopausal status and time spent in outdoor leisure-time activities, the inverse association between calcium intake and lung cancer risk was observed, although statistical significance was lost in some subgroups (data not shown).

Discussion

In our study, dietary calcium, phosphorus, and dairy food intakes and the Ca:Mg ratio were inversely associated with the risk of lung cancer among female non-smokers with relatively low calcium intake. The inverse associations for calcium intake with further adjustment for magnesium or soy food intake and for the Ca:Mg ratio with further adjustment for phosphorus or soy food intake remained statistically significant. There was no statistically significant association between use of calcium- or vitamin D-containing supplements and lung cancer risk.

Previously, one case-control and two cohort studies investigated the association between calcium intake and lung cancer risk (7-9). Consistent with our finding, one large cohort study in the United States reported an inverse association of dietary calcium intake with lung cancer risk among women [HR = 0.82 comparing the highest quartile of intake (>952 mg/ day) with the lowest (535 mg/day); 95% CI: 0.69, 0.97; 3,621 cases], which was borderline significant among all participants [HR = 0.92; 95% CI: 0.84, 1.01; 7,052 cases] (8). Similar results were reported in another report from the same cohort (6). The other large cohort study conducted in Germany reported a non-significant inverse association [HR = 0.71; 95% CI: 0.41, 1.21 comparing the highest quartile of calcium intake (mean intake: 1,131 mg/day) with the lowest (mean intake: 512 mg/day); 147 cases] (7). In contrast, the case-control study in the United States (923 cases and 1,125 matched controls) reported an overall significant positive association of dietary calcium intake with lung cancer [odds ratio = 1.64; 95% CI: 1.17, 2.29 comparing the highest quintile (1014 mg/day) with the lowest (586 mg/day); *P* for trend = 0.005], which was also observed in subgroups of men and current smokers, but no association was observed for women (9). It is of note that all previous studies were conducted in populations where calcium intake is substantially higher than in our study population and fortification of foods with vitamin D is relatively common. Our study population had lower calcium intake (median dietary calcium intake: 441 mg/day) than other study populations [medians: 770 mg/day (9) and 873 mg/day (8) in the United States; mean for second quartile: 675 and third quartile: 820 mg/day in Germany (7)]. Our median intake was closer to the 10th percentile of intake in a cohort study in the United

States (467 mg/day) (6), which reported a potential threshold for an inverse association between calcium intake and total cancer risk at 1,300mg/day, but no association at intakes above this level (6). To some extent, our finding was most similar to the inverse association for dietary calcium, not including intake from supplements, reported among women in the US study (8). In our study, further adjustment for dairy food intake attenuated, but did not eliminate the inverse association between dietary calcium and lung cancer risk. This suggests that dairy food intake may partially explain the observed inverse association. On the other hand, it is possible that a threshold effect for calcium intake or differential effects between calcium from foods and supplements may exist with regard to lung cancer risk, which might explain the discrepant associations reported across studies. In addition, most previous studies included very few never smokers. This also may explain the discrepancy given the potential differences in etiology between adenocarcinoma, which is common among non-smokers, and squamous cell carcinoma, which is more common among smokers. Nonetheless, more studies are needed to clarify the effect of calcium on lung cancer risk, especially in subgroups, such as women and never smokers.

Our finding of no association of lung cancer risk with the use of vitamin D-containing supplements is consistent with a previous study in the NHANES population and a case-control study nested within the ATBC study, which found no overall association between serum 25-hydroxyvitamin D concentration and the risk of lung cancer mortality (10) or incidence (12), respectively. Further, in the NHANES study, there was a positive association for men, but no association for women (10). In contrast, a Finnish cohort study reported an inverse association among women, but not among men (11). Secondary analysis of the Women's Health Initiative Clinical Trial showed a non-significantly lower risk of invasive lung cancer for women who took calcium and vitamin D supplements compared with those who did not (HR = 0.86; 95% CI: 0.67, 1.12) (2). Risk estimates were not provided by smoking status for this analysis (2). Another clinical trial of calcium and vitamin D supplements reported a smaller number of lung cancer cases in the group given both supplements (1 case), compared with the placebo (3 cases) and calcium only (3 cases) groups (22). During the time of our baseline survey, when the FFQ was administered, the fortification of the food supply with vitamin D in Shanghai, China was uncommon. This, along with low sunlight exposure and relatively dark skin, may have resulted in an average vitamin D concentration among women in our study population [median plasma concentration: 33.6 nmol/L (14)] that was lower than that reported for US women [mean serum concentration: 69.9 nmol/L among women in the NHANES III population (23)]. However, the circulating vitamin D level in our study population was relatively similar to the Finnish cohort [mean serum concentration: 38.1 nmol/L among women (11)]. Hence, the discrepant associations reported across studies might not be fully explained by differences in 25-hydroxyvitamin D concentration.

Our null finding on the association between dietary magnesium intake and lung cancer risk after adjustment for calcium intake is in agreement with the finding of a cohort study in Germany (7). In contrast, the cohort study in the United States reported a positive association for dietary magnesium intake overall and in subgroups, such as men and current smokers (8), after adjusting for total calcium intake. Magnesium intake in our study population was fairly similar to the US population. Hence, intake level may not be an explanation. Smoking status, other nutrients correlated with magnesium, such as calcium, or other unmeasured factors might have contributed to the inconsistent findings across studies. The Ca:Mg ratio is substantially higher in the US population (24) than that in the Chinese population, and this ratio may influence calcium absorption, since both minerals compete for intestinal absorption (25). To our knowledge, our study is the first to investigate the Ca:Mg ratio in relation to lung cancer and to report an inverse association. This finding is consistent with a US study of colorectal adenoma that found an inverse association (13). These

findings suggest the importance of considering other mineral intakes when assessing the association of calcium intake and cancer risk.

For strengths, to our knowledge, our study has the largest number of lung cancer cases among female non-smokers. In comparison with previous studies, our participants had lower calcium intake with a smaller proportion of calcium supplement users, which facilitated evaluations of dietary calcium intake and the potential threshold effect, if it exists. Note that the median intake in our study population was well below the recommended dietary allowance for calcium in the United States (1,000 mg/day for women 31-50 years old and 1,200 mg/day for women 51-70 years old). For limitations, our study did not collect dosage information on supplements or information on vitamin D fortification of foods, although the latter was not common during the time of our baseline survey. In addition, information on the vitamin D content of foods is not currently available in the Chinese Food Composition Tables. Thus, we were not able to compute the total intake of calcium from foods and supplements or dietary or total intake of vitamin D. Our study was also limited by a lack of direct information on sunlight exposure, although we used time spent in outdoor activities as a surrogate. Future studies with direct measurement of circulating 25-hydroxyvitamin D are needed. Another concern is multicollinearity, because calcium, phosphorus, and magnesium intakes are highly correlated. Hence, our study was limited in its ability to accurately assess the independent effect of these nutrients.

In summary, our study provides some of the first evidence suggesting a possible role for calcium in lung cancer among female non-smokers, particularly in populations where calcium intake level is relatively low and fortification of the food supply with vitamin D is uncommon.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of the study population[1]

	Non-Cases	Cases	*P*-value
Number of participants	70,839	428	-
Age at baseline (years)	52.3 ± 8.97	59.1 ± 8.58	<.0001
Education			
Elementary school or less	20.4%	21.3%	
Middle school	37.5%	38.9%	
High school	28.3%	26.8%	
Professional education/college or more	13.8%	13.0%	0.92
Income (per household)			
<10,000 yuan	15.7%	15.6%	
10,000-20,000 yuan	38.2%	34.9%	
20,000-30,000 yuan	28.3%	31.4%	
30,000 yuan	17.8%	17.9%	0.71
Occupation			
Housewife	0.3%	0.2%	
Professional workers	29.0%	30.5%	
Clerical workers	20.7%	20.4%	
Manual laborers	50.0%	48.9%	0.88
Family history			
Any cancer	26.6%	28.7%	0.66
Lung cancer	4.9%	6.4%	0.18
Personal history of lung disease			
Tuberculosis	5.5%	7.5%	0.61
Chronic bronchitis	7.3%	7.3%	0.75
Asthma	2.1%	3.5%	0.09
BMI (kg/m^2)	24.0 ± 0.01	23.9 ± 0.16	0.38
Waist-to-hip ratio	0.810 ± 0.0002	0.811 ± 0.0025	0.86
Passive smoking			
None	19.8%	20.8%	
At home or in workplace	52.4%	48.5%	
Both	27.9%	30.7%	0.79
Ever consumed alcohol	1.9%	1.0%	0.51
Ever consumed tea	29.5%	30.6%	0.15
Postmenopausal status	48.2%	49.3%	0.47

	Non-Cases	Cases	P-value
Supplement use			
Any vitamin	19.6%	19.9%	0.62
Calcium-containing[2]	36.1%	31.8%	0.06
Vitamin D-containing[2]	20.2%	19.0%	0.05
Regular exercise[3]	35.0%	33.3%	0.81

[1]Adjusted for age at baseline and presented as mean ± standard error or frequency (%), except for age at baseline where unadjusted mean ± standard deviation is shown.

[2]45 cases and 5,484 non-cases had missing information for calcium- and vitamin D-containing supplement use and were included in a separate category.

[3]Defined as at least once per week continuously for at least three months within the five years before the interview.

Table 2

Age- and total energy intake-adjusted nutrient and dairy food intakes at baseline[1]

	Non-cases	**Cases**	***P*-value**
Total energy (Kcal/day)[2]	1677 ± 1.5	1675 ± 19.1	0.92
Nutrients			
Fat (g/day)	29.5 ± 0.03	28.5 ± 0.44	0.03
Protein (g/day)	67.3 ± 0.04	66.5 ± 0.54	0.19
Carbohydrates (g/day)	285.6 ± 0.11	288.4 ± 1.39	0.04
Fiber (g/day)	11.0 ± 0.01	11.0 ± 0.16	0.88
Calcium (mg/day)	467 ± 0.62	446 ± 8.01	0.01
Magnesium (mg/day)	277 ± 0.17	275 ± 2.16	0.49
Phosphorus (mg/day)	969 ± 0.55	956 ± 7.12	0.07
Ca:Mg ratio	1.657 ± 0.002	1.584 ± 0.021	0.0004
Foods			
Any dairy food intake	56.7%	54.2%	0.03

[1] Data are presented as mean ± standard error

[2] Adjusted for age only

Table 3

Lung cancer risk associated with dietary intakes of calcium and related minerals[1]

Nutrient	Quartiles	Median	Range	Cases	HR	95% CI		P-trend
Calcium (mg/day)	1	254	<321	136	Reference			
	2	382	321-441	112	0.90	0.70,	1.17	
	3	504	441-578	95	0.77	0.58,	1.02	
	4	687	>578	85	**0.66**	**0.48,**	**0.91**	**0.007**
Magnesium (mg/day)	1	193	<222	130	Reference			
	2	244	222-266	93	0.79	0.59,	1.05	
	3	290	266-319	110	0.95	0.69,	1.30	
	4	365	>319	95	0.81	0.54,	1.23	0.50
Phosphorus (mg/day)	1	669	<773	140	Reference			
	2	855	773-935	93	**0.68**	**0.51,**	**0.91**	
	3	1021	935-1124	111	0.81	0.59,	1.11	
	4	1286	>1124	84	**0.55**	**0.36,**	**0.85**	**0.02**
Ca:Mg ratio	1	1.18	<1.33	142	Reference			
	2	1.47	1.33-1.61	95	**0.75**	**0.58,**	**0.97**	
	3	1.78	1.61-1.96	109	0.87	0.68,	1.12	
	4	2.17	>1.96	82	**0.62**	**0.47,**	**0.82**	**0.003**

[1] Adjusted for age, total caloric intake, income, occupation, passive smoking, history of asthma and BMI. The median value of each quartile was used to test for linear trend.

Table 4

Lung cancer risk associated with calcium- or vitamin D-containing supplement use or by dairy food intake[1]

Use/Intake		Cases	HR	95% CI		*P*-value
Calcium-containing supplements[2]	No	239	Reference			
	Yes	144	0.89	0.72,	1.10	0.28
Vitamin D-containing supplements[2]	No	290	Reference			
	Yes	93	1.11	0.87,	1.41	0.40
Dairy foods[3]	None	229	Reference			
	Any	199	**0.79**	**0.65,**	**0.96**	**0.02**

[1] Adjusted for age, total caloric intake, income, occupation, passive smoking, history of asthma, and BMI.

[2] 45 cases and 5,484 non-cases had missing information for calcium- and vitamin D-containing supplement use and were included in a separate category.

[3] An y intake from fresh milk and/or milk powder

Table 5

Joint effects of dietary calcium and calcium- and/or vitamin D-containing supplement use on lung cancer risk[1,2]

Dietary calcium	Range (mg/day)	Use of calcium-containing supplements						P interaction
		No			Yes			
Quartile		Cases	HR	95% CI	Cases	HR	95% CI	
1	<321	82	Reference		40	1.13	0.77, 1.65	
2	321-441	70	1.06	0.77, 1.47	34	0.82	0.55, 1.24	
3	441-578	47	0.81	0.56, 1.17	34	0.71	0.47, 1.08	
4	>578	40	0.77	0.51, 1.17	36	0.65	0.42, 1.00	
								0.58

		Use of vitamin D-containing supplements						P interaction
		No			Yes			
Quartile		Cases	HR	95% CI	Cases	HR	95% CI	
1	<321	98	Reference		24	1.53	0.98, 2.40	
2	321-441	87	1.04	0.77, 1.40	17	0.85	0.50, 1.43	
3	441-578	59	0.79	0.56, 1.11	22	0.81	0.50, 1.30	
4	>578	46	0.66	0.44, 0.98	30	0.88	0.56, 1.37	
								0.28

		Use of calcium- and vitamin D-containing supplements						P interaction
		Neither			Either or both			
Quartile		Cases	HR	95% CI	Cases	HR	95% CI	
1	<321	82	Reference		40	0.92	0.63, 1.35	
2	321-441	69	0.75	0.48, 1.19	35	0.97	0.65, 1.44	
3	441-578	45	0.67	0.42, 1.06	36	0.73	0.47, 1.13	
4	>578	38	0.60	0.37, 0.97	38	0.69	0.37, 0.97	
								0.69

[1] Adjusted for age, total caloric intake, income, occupation, passive smoking, history of asthma, and BMI. The median value of each quartile was used to test for a linear trend.

[2] 45 cases and 5,484 non-cases had missing information for calcium- and vitamin D-containing supplement use and were excluded from the analysis.