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Dietary B vitamin and methionine intakes and lung cancer risk among female never smokers in China

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Abstract

Purpose—B vitamins and methionine have been postulated to have potential effects on carcinogenesis; however, findings from previous epidemiologic studies on B vitamins, methionine, and lung cancer risk are inconsistent. We investigated associations of dietary intakes of B vitamins (i.e., riboflavin, niacin, vitamin B6, folate, and vitamin B12) and methionine with lung cancer risk among female never smokers.

Methods—The Shanghai Women's Health Study, a population-based, prospective cohort study, included 74,941 women. During a median follow-up of 11.2 years, 428 incident lung cancer cases accrued among 71,267 women with no history of smoking or cancer at baseline. Baseline dietary intakes were derived from a validated, interviewer-administered food frequency questionnaire. Cancer incidence and vital status were ascertained through annual linkage to the Shanghai Cancer Registry and Shanghai Vital Statistics Registry databases and through biennial in-person follow-ups with participants. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox regression.

Results—Dietary riboflavin intake was inversely associated with lung cancer risk (HR = 0.62; 95% CI = 0.43–0.89; *P*-trend = 0.03 for the highest quartile compared with the lowest). A higher than median intake of methionine was associated with lower risk of lung cancer (HR = 0.78; 95% CI = 0.60–0.99), however, there was no dose-response relation. Intakes of other B vitamins were not associated with lung cancer risk.

Conclusions—Our study suggests that dietary riboflavin intake may be inversely associated with lung cancer risk among female never smokers, which warrants further investigation.

Keywords

B vitamins; methionine; lung cancer; never smokers; women

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Introduction

Folate and methionine, as methyl group donors, and riboflavin, vitamin B6, and vitamin B12, as cofactors in one-carbon metabolism, are linked to DNA synthesis and methylation and, hence, may play a role in carcinogenesis. Based on its role in DNA repair by nicotinamide adenine dinucleotide, niacin may also affect carcinogenesis [1,2]. Inverse associations of folate intake or serum folate, vitamin B6, and methionine concentration with lung cancer risk have been reported in a few case-control studies [3–5]. In contrast, secondary analysis of a clinical trial [6] and the majority of cohort studies have observed no association between intakes or blood concentrations of B vitamins with lung cancer risk [7–11], except for one cohort study that observed a positive association for dietary folate intake [12]. Furthermore, few studies have investigated the association of B vitamins other than folate or methionine with lung cancer risk among subgroups such as never smokers [5] and women [8]. These studies yielded inconclusive evidence.

The majority of previous studies were conducted in North America and Europe, where B vitamin fortification of the food supply and smoking among women are relatively more common than in other populations, such as China. The Shanghai Women's Health Study (SWHS), a population-based, prospective cohort study of middle-aged and elderly women in Shanghai, China, accrued 428 lung cancer cases among female never smokers, the largest number of such cases in any study conducted to date, including a previous pooled analysis of eight prospective studies (259 cases among male and female never smokers combined) [7]. While the major risk factor for lung cancer is smoking, lung cancer does occur in never smokers and risk factors for lung cancer among them are not well understood [13]. Using data from the SWHS, we investigated whether dietary intakes of B vitamins and methionine were associated with the risk of incident lung cancer among female never smokers in Shanghai, China, a population with one of the highest lung cancer incidence rates among never smokers.

Materials and Methods

Study population

The SWHS included 74,941 women aged 40 to 70 years who lived in urban Shanghai at the time of recruitment (March 1997 to May 2000) [14]. Eligible participants were identified through the Shanghai Resident Registry and were invited by trained interviewers to participate in the study. During home visits at baseline, trained interviewers administered questionnaires to participants in person and collected information regarding demographics, medical history, lifestyle, and dietary habits. Blood and urine samples were collected, and body weight, height, and waist and hip circumferences were measured. The last follow-up date included in the current analysis was December 31, 2009. All participants provided written, informed consent, and the study was approved by the Institutional Review Boards of all participating institutes.

Dietary intake assessment

Typical dietary intake during the year prior to study enrollment was assessed during the in-person interview using a quantitative food frequency questionnaire (FFQ) that included 77 food items that were commonly consumed in the study population. This FFQ was validated by multiple 24-hour dietary recalls in a subset of participants in the SWHS. Pearson correlation coefficients between FFQ and dietary recalls were 0.56 for riboflavin and 0.58 for niacin [15]. Daily intakes of total calories and nutrients, excluding vitamin B6, vitamin B12, and methionine, were estimated using the Chinese Food Composition Tables [16]. The

excluded nutrients were estimated using the United States Department of Agriculture Food Composition Database as previously described [17].

Cohort follow-up and lung cancer case ascertainment

Annual linkage of SWHS participant files to the Shanghai Cancer Registry and the Shanghai Vital Statistics Registry databases were conducted to ascertain cancer incidence and all-cause mortality. Further, vital status and self-reported diagnoses of cancer and chronic diseases were updated every 2–3 years via home visits. Cancer diagnoses ascertained by linkage were verified through in-person interviews. All cancer diagnoses were confirmed by medical chart review. Included in this analysis were 428 lung cancer cases (ICD-9 code: 162 [18]) confirmed among study participants after the baseline survey. There were 186 cases with adenocarcinoma, 13 cases with squamous cell carcinoma, 19 cases with adenosquamous carcinoma, 27 cases with other subtypes, and 183 cases with missing information for cancer subtype.

Statistical analysis

Statistical analyses were performed using SAS 9.2 (SAS Institute, Inc., Carey, NC) and STATA 11 (Stata Corporation, College Station, TX). Excluded from the current analyses were participants who met at least one of the following exclusion criteria: a history of cancer at baseline interview ($n = 1,579$), a history of smoking ($n = 2,042$), reported total caloric intake outside the range of 500 to 4,000 Kcal/day ($n = 45$), and no follow-up ($n = 8$). A total of 71,267 participants were included in the current analyses. Missing values for categorical variables, including education ($n = 13$), income ($n = 16$), history of lung disease ($n = 3$), and family history of cancer ($n = 1$), were replaced with the most common category. For body mass index (BMI), missing values at baseline were replaced with values reported in the follow-up survey in 2004 ($n = 8$) or the most common category (BMI of 20 to 23 kg/m²) ($n = 13$). Characteristics of the study population were compared between cases and non-cases and also by quartiles of riboflavin intake after adjusting for age at baseline. Intakes of fruits, vegetables, and nutrients were compared between cases and non-cases after further adjusting for total caloric intake. In order to explore food sources of B vitamins and methionine in our study population, the major food contributors to each B vitamin and methionine intake were calculated as the proportion of each food item contributing to the total daily intake of each nutrient. Spearman correlation coefficients were calculated for intakes of B vitamins and methionine, as well as between B vitamins or methionine and selected mineral intakes (i.e., calcium, phosphorus, and zinc) or intakes from 13 food groups (i.e., all vegetables; allium vegetables; cruciferous vegetables; green leafy vegetables; legumes, excluding soy; eggs; fish; poultry; red meat; rice; dairy; soy; and all fruit) after adjusting for total caloric intake.

Cox proportional hazards regression models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI). Quartiles for each nutrient were created based on its distribution in the entire cohort. Linear trends were evaluated based on the median values within each quartile. All analyses were adjusted for age at baseline (continuous), passive smoking (three categories including none, at household or workplace, or both locations), history of asthma (yes or no), occupation (three categories, including housewife/clerical workers, professional workers, or manual laborers), income (four categories ranging from <10,000 *yuan* to 30,000 *yuan*), total caloric intake (continuous), and BMI (five categories ranging from BMI < 23 to BMI 27.5 kg/m²). The following variables were considered to be potential covariates, however, due to their small effects on risk estimates, they were not included in the final model: menopausal status, hormone replacement therapy use (either peri- or postmenopausal), duration of hormone replacement therapy, history of tuberculosis or chronic bronchitis, and family history of cancer.

Given findings from recent cancer studies [5,19] and biological plausibility [20,21], the joint effects of folate intake with other nutrients (i.e., riboflavin, vitamin B6, vitamin B12, or methionine) or with the use of B vitamin-containing supplements [either from single B vitamin supplements (information on specific B vitamins was not collected) or multivitamin supplements] were investigated in relation to lung cancer risk. We created five variables for these joint effects and each variable had six categories defined by: 1) tertiles of dietary folate intake and 2) intake of the other B vitamins or methionine dichotomized at the median or by the use of B vitamin-containing supplements. Adjusted HRs and 95% CIs were calculated for each category using participants with the lowest tertile of folate intake and with below-median intake of other nutrients or non-users of B vitamin-containing supplements as the reference group. Interaction effects were tested by including the main effects and the product terms of folate and the other nutrient intakes or B vitamin-containing supplement use and assessing its *P*-value. Subgroup analyses were conducted among non-drinkers, those with no history of lung disease, non-users of B vitamin-containing supplements, and by passive smoking exposure. Sensitivity analyses were conducted by excluding the first two years of follow-up (320 deaths, 46 cases).

Meta-analysis of previous studies of riboflavin or folate intakes and lung cancer risk was conducted to compare our finding on riboflavin and folate with those from previous studies. We searched articles through PubMed using the keywords, “lung cancer” and “B vitamins”, “folate”, or “riboflavin” and selected observational studies. From each article, we retrieved the first author’s name, the publication year, the location of the study, the number of cases, the risk estimate of lung cancer comparing the highest with the lowest quantiles and the corresponding 95% confidence intervals, *P*-trend, and the median or mean intake or serum concentration in the study population. If stratified analyses by gender or smoking status were reported, information was retrieved separately for each. When a study reported risk estimates of lung cancer by dietary and supplement intakes separately, we included risk estimates using dietary intake in our meta-analysis, except for the meta-analysis in which we specifically evaluated the association for supplement intakes. Summary estimates [odds ratio (OR) and 95% CIs] from previous studies were calculated through a random-effects meta-analysis model [22,23]. The I^2 statistic was used to assess heterogeneity across studies and the *P*-value was calculated based on Cochran’s *Q* statistics [24]. We stratified analyses by studies that assessed dietary intake, supplement intake, or serum concentration of folate, by cohort studies and case-control studies, and among never smokers.

Results

During a median follow-up of 11.2 years, 428 participants were diagnosed with lung cancer. Cases were older than non-cases (Table 1). No significant differences were found between cases and non-cases for education, income, occupation, anthropometric characteristics (BMI and waist-to-hip ratio), passive smoking exposure, alcohol consumption, or vitamin supplement use. History of lung disease was also similar between cases and non-cases, although more cases had a history of asthma than non-cases. There were 21 cases diagnosed with lung cancer during the first year of follow-up and 25 cases diagnosed during the second year of follow-up. When baseline characteristics were compared by quartiles of riboflavin intake, women in higher quartiles tended to be younger, have higher socioeconomic status, and have less passive smoking, compared with those in lower quartiles (Supplementary Table 1). In addition, more women in higher quartiles had a history of lung disease, took vitamin supplements, and exercised regularly, than those in lower quartiles.

Cases and non-cases had similar total caloric intake (Table 2). Cases had slightly lower intake of fat and higher intake of carbohydrates than non-cases, while protein intake was similar. Cases had lower intake of riboflavin compared with non-cases and the difference

was statistically significant ($P = 0.03$), whereas intakes of the other B vitamins and methionine were similar between the two groups. There were strong correlations between several B vitamin and methionine intakes (Table 3); the strongest correlation was observed between vitamin B12 and methionine ($r = 0.82$), followed by the correlations between niacin and methionine and between riboflavin and vitamin B12 ($r = 0.73$ for both). In contrast, the correlations of B vitamins and methionine with food group intakes were lower, with correlation coefficients ranging from -0.01 to 0.71 . The major food contributors to riboflavin intake were rice, fresh milk, eggs, and bok choy (data not shown). For the rest of the B vitamins and methionine, the major food contributors included rice, fresh pork, eggs, fresh milk, saltwater fish, and soy milk. Rice, as the major staple in China, was a major food contributor to all B vitamins and methionine intakes. However, it was inversely correlated with these nutrient intakes, since women with higher rice intake had lower intakes of other food items that contain these nutrients than those who consumed less rice. Rice intake constituted 19.5% of total riboflavin intake. Among women in the first to third quartiles of riboflavin intake, rice was the major food contributor; however, among women in the fourth quartile, fresh milk and eggs were the two major food contributors and rice was the third major contributor.

Dietary intake of riboflavin was inversely associated with lung cancer risk; the highest quartile was associated with 38% lower risk than the lowest quartile (HR = 0.62; 95% CI = 0.43–0.89; P -trend = 0.03) (Table 4). Analyses excluding the first two years of observation (46 cases, 320 deaths) did not appreciably change the risk estimates. Further adjustment for folate intake slightly strengthened the association of riboflavin intake with lung cancer risk (HR = 0.54; 95% CI = 0.36–0.82), while adjustment for calcium (HR = 0.88; 95% CI = 0.52–1.49), phosphorus (HR = 0.76; 95% CI = 0.47–1.23), or zinc intake (HR = 0.67; 95% CI = 0.45–1.01) attenuated the association. The correlations between riboflavin intake and intakes of calcium, phosphorus, and zinc were 0.81, 0.80, and 0.60, respectively (Table 3). The inverse association for vitamin B12 intake was marginally significant for the highest quartile of intake compared with the lowest (HR = 0.76; 95% CI = 0.55–1.05) (Table 4). Although there was no linear trend (P -trend = 0.26), since the participants in the highest two quartiles of methionine intake also had lower lung cancer risk, the analyses were repeated by dichotomizing at the median intake. Intake of methionine above the median was associated with a 22% lower risk than intake below the median (HR = 0.78; 95% CI = 0.60–0.99) (data not shown in table).

The use of B vitamin-containing supplements was not significantly associated with lower lung cancer risk (HR = 0.87; 95% CI = 0.64–1.19) (data not shown in table). There were no associations between food group intakes and lung cancer risk, except for an inverse association for intakes of dairy food (Supplementary Table 2) and soy food that we reported in another publication [25]. Further adjustment for major food contributors to riboflavin intake did not materially change the association for riboflavin intake, except for dairy intake, where inverse associations of both riboflavin and dairy intakes with lung cancer risk were attenuated and no longer statistically significant. Among individual food items that contributed considerably to intakes of B vitamins and/or methionine (rice, fresh pork, eggs, fresh milk, saltwater fish, and soy milk), intake of saltwater fish was positively associated with lung cancer risk (HR = 1.34; 95% CI = 0.97–1.86; P -trend = 0.04) for the highest quartile compared with the lowest. No other individual food item was associated with lung cancer risk (data not shown).

Analyses stratified by subgroups, including non-users of B vitamin-containing supplements, non-drinkers of alcohol, those with no history of lung disease, and those with or without passive smoking exposure (none, at either household or workplace, or both), generally did not alter the direction or statistical significance of the aforementioned associations (data not

shown). However, the inverse association for riboflavin became stronger among non-users of B vitamin-containing supplements (HR = 0.55; 95% CI = 0.37–0.82; P -trend = 0.01; 383 cases). Furthermore, no clear patterns were generally observed for joint associations of folate and dietary B vitamins or methionine (Table 5). Although the number of cases for some categories was relatively small, there was a significant interaction effect for the joint effects of folate and vitamin B6 intakes (P -interaction = 0.04).

In our meta-analysis of three previous studies [5,8,26], riboflavin intake was not associated with lung cancer risk (OR = 1.06; 95% CI = 0.88–1.28 for the highest quantile compared with the lowest) with no evidence of heterogeneity (I^2 = 51.6%; P -heterogeneity = 0.13) (Table 6, Supplementary Figure 1). For folate, self-reported intake was not associated with lung cancer risk (OR = 0.94; 95% CI = 0.85–1.03) with some evidence of heterogeneity across studies [3,7,8,10–12,26–30] (I^2 = 52.0%; P -heterogeneity = 0.03) (Table 6, Supplementary Figure 2A). To further elucidate the heterogeneity observed among these studies, we conducted stratified analyses. When we stratified by the source of folate intake (from diet or supplements), no association was observed for either studies of dietary intake (OR = 0.96; 95% CI = 0.86–1.07; I^2 = 32.5%; P -heterogeneity = 0.18) or studies of supplement intake [10,12] (OR = 0.97; 95% CI = 0.81–1.16; I^2 < 0.01%; P -heterogeneity = 0.79). When stratified by study design, an inverse association was observed among case-control studies [3,27] (OR = 0.68; 95% CI = 0.50–0.92; I^2 = 65.8%; P -heterogeneity = 0.09) (Supplementary Figure 2B), but not among cohort studies [7,8,10–12,26,29] (OR = 0.97; 95% CI = 0.88–1.07; I^2 = 32.0%; P -heterogeneity = 0.18) (Supplementary Figure 2C). Hence, study design might be a source of heterogeneity. For studies that measured serum folate concentrations [4,5,9,31], the inverse association was borderline significant (OR = 0.76; 95% CI = 0.58–1.00; I^2 < 0.01%; P -heterogeneity = 0.78). Among never smokers [5,7,11], there was no association (OR = 0.76; 95% CI = 0.50–1.14; I^2 < 0.01%; P -heterogeneity = 0.91) (Supplementary Figure 2D).

Discussion

In this large prospective cohort study of middle-aged and elderly female never smokers in China, dietary intake of riboflavin was inversely associated with lung cancer risk. This association was more pronounced among women who did not take B vitamin-containing supplements. A higher than median intake of methionine was associated with lower risk of lung cancer. Our meta-analysis of previous studies showed no overall associations of lung cancer risk with riboflavin or folate.

Riboflavin is the central component of flavin mononucleotides and flavin dinucleotides, coenzymes for a wide variety of oxidative enzymes, including methylenetetrahydrofolate reductase [32]. Our finding for riboflavin intake is consistent with a previous study that observed an inverse association among current smokers (155 cases), but not among past (143 cases) or never smokers (50 cases) [26], and two case-control studies, one conducted in the United States among past smokers (470 cases) [3] and the other in Taiwan that measured red blood cell riboflavin concentrations (50 cases) [33]. However, two studies, including one conducted among women, reported a positive association with dietary intake [5,8]. Inconsistent with our study finding of an inverse association, our meta-analysis of three previous studies of riboflavin intake [5,8,26] (Table 6, Supplementary Figure 1) and two studies of serum riboflavin [5,6] found no association. The average riboflavin intake level in our population was much lower than in previous studies reporting positive and inverse associations [8,26]. Therefore, the observed differences cannot be entirely explained by differences in intake levels. Additionally, in our study, the association with riboflavin was attenuated substantially after adjustment for intakes of calcium, phosphorus, or zinc. Given the high correlations between riboflavin and these mineral intakes, it is possible that our

observed association for riboflavin might be due to these correlations and riboflavin might have served as a surrogate for these minerals. Our finding for methionine intake is consistent with findings from a large prospective study that reported an inverse association for serum methionine concentrations [5], but not with two other studies using dietary intake [8,26]. Since we did not observe a dose-response relation, this finding warrants further investigation.

Lack of an association between folate intake and lung cancer risk in our study is consistent with our meta-analysis of previous observational studies using self-reported dietary and/or supplement intakes [3,7,8,10–12,26–30], especially cohort studies, but not with our meta-analysis of case-control studies that observed an inverse association [3,27] (Table 6, Supplementary Figure 2). Moreover, our meta-analysis of four previous studies that measured serum folate concentration showed a borderline significant inverse association [4,5,9,31]. Consistent with our study finding, no association was observed among never smokers in the meta-analysis of three previous studies [5,7,11]. Given that a relatively small number of previous studies conducted stratified analyses by smoking status or gender and that these analyses were often not well powered, the effects of gender and smoking on the association of folate with lung cancer need to be further elucidated.

Consistent with two previous studies, including the European Prospective Investigation into Cancer and Nutrition (EPIC) [5,26], our study found no association between dietary intake of vitamin B6 and lung cancer risk. In contrast, two previous prospective studies that measured vitamin B6 concentration in serum reported a significant inverse association [4,5]. The inconsistent findings between self-reported and serum vitamin B6 measurements reported in the EPIC study [5] are probably due to a low correlation between these measurements ($r = 0.11$). Our study also suggests there may be an interaction effect of folate and vitamin B6 intakes on lung cancer risk. Since we had a small number of cases in the first tertile and high vitamin B6 category ($n = 13$), this finding needs to be re-evaluated when more lung cancer cases accrue.

For vitamin B12, both serum concentration and self-reported dietary intake were positively associated with lung cancer risk in previous studies; the associations were significant in the EPIC study [5] and non-significant in other prospective studies [4,26]. Therefore, our finding of no overall significant inverse association is generally inconsistent with these findings. This could be due to lower B12 intake (mean = 2.6 $\mu\text{g/day}$) in our study than those reported in previous studies (mean intake range: 3.6 to 11.0 $\mu\text{g/day}$) [4,5,26].

In our analysis of food group intake and lung cancer risk, we found a positive association with saltwater fish intake, which was a major contributor to vitamin B12 and methionine intakes. However, there was no association with total fish intake, which is consistent with a recent meta-analysis that reported no association between fish intake and lung cancer risk [34]. Since many hypotheses were tested in our analysis, this finding may be due to chance and needs to be confirmed in other studies.

For strengths, our study is one of the largest studies of lung cancer among women, especially female never smokers [7]. It is also a prospective cohort study conducted in an area where folic acid and other B vitamin fortification of the food supply, the use of B vitamin and multivitamin supplements, and alcohol consumption among women are relatively uncommon. Hence, B vitamin intakes in our study were lower than those reported in previous studies [8,12,26,30]. Since this might have resulted in a stronger association in our study, the generalizability of our findings to populations with higher intakes than ours may be limited. A limitation of our study is that intakes of vitamin B6, vitamin B12, and methionine were estimated based on the United States Department of Agriculture Food

Composition Database, because these nutrients were not included in the Chinese Food Composition Tables. Our study is also limited by a lack of information on known polymorphisms in genes related to one-carbon metabolism, such as *MTHFR* [35], that have been reported to interact with the association of riboflavin and/or folate with cancer risk [36] or homocysteine concentrations [21].

In conclusion, our study, conducted in a population where intakes of B vitamins are relatively low, suggests an inverse association of riboflavin with lung cancer risk among female never smokers. Since findings from self-reported dietary intake and biomarker studies are generally inconsistent and nutrient-gene interactions in one-carbon metabolism have been reported, future studies are needed that include measurement of biomarkers of B vitamins and methionine, as well as consideration of genetic variants when investigating the association of B vitamins and methionine with lung cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1Baseline Characteristics of the Study Population¹

	Non-Cases	Cases	P-value
Number	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			
<10,000 <i>yuan</i>	15.7%	15.7%	
10,000–20,000 <i>yuan</i>	38.2%	34.9%	
20,000–30,000 <i>yuan</i>	28.3%	31.4%	
30,000 <i>yuan</i>	17.8%	18.0%	0.69
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 of any cancer	26.6%	28.7%	0.66
Family history of 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 household or 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	51.8%	50.7%	0.47
Vitamin supplement use			
B vitamin-containing	10.4%	10.0%	0.39

	Non-Cases	Cases	P-value
Any vitamin	19.6%	19.9%	0.62
Regular exercise ²	35.0%	33.3%	0.81

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

² Defined as at least once per week continuously for at least three months within the past five years.

Table 2Baseline Nutrient and Food Intakes of the Study Population[/]

	Non-cases	Cases	P-value
Number	70,839	428	-
Total calories (Kcal/day)	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
Riboflavin (mg/day)	0.85 ± 0.001	0.83 ± 0.011	0.03
Niacin (mg/day)	14.3 ± 0.01	14.3 ± 0.11	0.83
Vitamin B6 (mg/day)	1.70 ± 0.001	1.71 ± 0.018	0.51
Folate (µg/day)	291.4 ± 0.3	291.4 ± 3.9	0.999
Vitamin B12 (µg/day)	2.61 ± 0.01	2.53 ± 0.07	0.22
Methionine (g/day)	1.52 ± 0.001	1.50 ± 0.015	0.31

[/] Adjusted for age and total caloric intake, except for total caloric intake, which was adjusted for age and presented as mean ± standard error.

Table 3
Spearman Correlations among B Vitamin Intakes and between B Vitamins and Food Group Intakes[/]

	Riboflavin	Niacin	Vitamin B6	Folate	Vitamin B12	Methionine
Nutrients						
Riboflavin	-					
Niacin	0.50	-				
B6	0.65	0.71	-			
Folate	0.54	0.40	0.62	-		
B12	0.73	0.54	0.43	0.28	-	
Methionine	0.64	0.73	0.55	0.39	0.82	-
Calcium	0.81	0.32	0.52	0.51	0.51	0.54
Phosphorus	0.80	0.62	0.62	0.63	0.69	0.83
Zinc	0.60	0.75	0.63	0.57	0.51	0.74
Food groups						
All vegetables	0.49	0.50	0.67	0.61	0.17	0.26
Allium vegetables	0.18	0.21	0.29	0.23	0.12	0.15
Cruciferous vegetables	0.33	0.32	0.47	0.43	0.05	0.13
Green leafy vegetables	0.21	0.24	0.28	0.27	0.11	0.16
Legumes	0.26	0.34	0.37	0.44	0.10	0.19
Eggs	0.42	0.07	0.15	0.31	0.46	0.38
Fish	0.39	0.53	0.39	0.23	0.71	0.70
Poultry	0.28	0.46	0.27	0.08	0.32	0.40
Red meat	0.19	0.51	0.28	-0.02	0.32	0.45
Rice	-0.70	-0.57	-0.68	-0.48	-0.58	-0.67
Dairy ²	0.63	-0.01	0.11	0.02	0.44	0.27
Soy ²	0.16	0.16	0.23	0.53	0.06	0.32
All fruits	0.41	0.25	0.63	0.37	0.20	0.13

[/] Adjusted for total caloric intake. $P < 0.0001$ for all correlations.

² Since the water content of soy and dairy food items varies, total soy intake was calculated in dry weight, as we previously described [25], and total dairy intake was calculated as a sum of fresh milk intake and the liquid equivalent of fresh milk intake based on milk powder intake (only two dairy items were included in our FFQ).

Table 4

Risk of Lung Cancer by Dietary Intakes of B Vitamins and Methionine[/]

Nutrient	Quartiles	Median	Cases	HR	95% CI	P-trend
Riboflavin (mg/day)	1	0.52	144	Reference		
	2	0.72	102	0.82	0.63, 1.07	
	3	0.91	110	0.92	0.69, 1.22	
	4	1.20	72	0.62	0.43, 0.89	0.03
Niacin (mg/day)	1	9.91	119	Reference		
	2	12.5	116	1.14	0.86, 1.52	
	3	14.9	110	1.17	0.84, 1.64	
	4	18.9	83	0.94	0.60, 1.49	0.76
Vitamin B6 (mg/day)	1	1.12	126	Reference		
	2	1.47	113	1.14	0.87, 1.49	
	3	1.79	88	0.97	0.71, 1.33	
	4	2.32	101	1.21	0.84, 1.74	0.44
Folate (µg/day)	1	185	129	Reference		
	2	248	85	0.76	0.57, 1.01	
	3	308	111	1.02	0.77, 1.34	
	4	405	103	0.96	0.70, 1.32	0.79
Vitamin B12 (µg/day)	1	1.03	152	Reference		
	2	1.91	97	0.80	0.61, 1.04	
	3	2.75	104	0.95	0.72, 1.25	
	4	4.27	75	0.76	0.55, 1.05	0.19
Methionine (g/day)	1	0.99	128	Reference		
	2	1.31	126	1.14	0.87, 1.49	
	3	1.60	87	0.84	0.61, 1.16	
	4	2.08	87	0.87	0.58, 1.29	0.26

[/] Adjusted for age (continuous), passive smoking (none, at household or workplace, or both locations), total caloric intake (continuous), income (four categories ranging from <10,000 *yuan* to 30,000 *yuan*), occupation (housewife/clerical workers, professional workers, or manual laborers), BMI category (five categories ranging from BMI <23 to BMI ≥27.5 kg/m²), and history of asthma (yes or no).

Table 5

Joint Effects of Folate, Other B Vitamins, and Methionine on Lung Cancer Risk[/]

Dietary folate intake										
Tertile 1 (Low)			Tertile 2 (Medium)			Tertile 3 (High)				
Intake	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI	P-interaction
Riboflavin										
Low	140		Reference	72	0.93	0.70, 1.25	34	1.13	0.77, 1.65	
High	17	0.80	0.48, 1.34	60	0.92	0.66, 1.27	105	0.94	0.69, 1.31	0.75
Vitamin B6										
Low	144		Reference	62	0.88	0.65, 1.19	33	1.52	1.04, 2.24	
High	13	1.32	0.63, 2.00	70	1.03	0.75, 1.41	106	0.97	0.70, 1.27	0.04
Vitamin B12										
Low	124		Reference	75	1.03	0.77, 1.38	50	1.06	0.75, 1.51	
High	33	1.09	0.73, 1.61	57	0.92	0.65, 1.29	89	1.05	0.75, 1.47	0.75
Methionine										
Low	133		Reference	82	1.14	0.87, 1.51	39	1.28	0.89, 1.85	
High	24	1.16	0.74, 1.82	50	0.72	0.50, 1.04	100	0.88	0.62, 1.24	0.08
B vitamin-containing supplement use										
None	149		Reference	115	0.91	0.71, 1.18	119	0.98	0.74, 1.31	
Any	8	0.50	0.24, 1.01	17	0.95	0.57, 1.59	20	1.03	0.63, 1.68	0.18

[/] Adjusted for age (continuous), passive smoking (none, at household or workplace, or both locations), total caloric intake (continuous), income (four categories ranging from <10,000 *yuan* to 30,000 *yuan*), occupation (housewife/clerical workers, professional workers, or manual laborers), BMI category (five categories ranging from BMI < 23 to BMI ≥ 27.5 kg/m²), and history of asthma (yes or no).

Table 6

Previous Studies of Riboflavin, Folate, and Lung Cancer Risk

First author, publication year	Country	Study design	Gender	Smoking status	Cases	Measure	Mean/median intake/conc.	Risk estimates ¹	P-trend
Riboflavin									
Bassett 2011[26]	Australia	Cohort	Both	All	348	Diet	2.5 mg/day	0.79 (0.55, 1.13)	0.15
				Never	50			1.03 (0.44, 2.42)	0.82
				Past	143			1.00 (0.59, 1.71)	0.84
				Current	155			0.53 (0.29, 0.94)	0.01
Kabat 2008[8]	Canada	Cohort	Women	All	358	Diet	1.63 mg/day	1.30 (0.94, 1.80)	0.08
Johansson 2010[5]	Europe	Nested	Both	All	899	Diet	1.68 mg/day	1.10 (0.81, 1.49)	0.50
		case-control	Both	All	899	Serum	19.8 nmol/L	0.82 (0.61, 1.09)	0.11
				Never	96			0.96 (0.48, 1.91)	0.38
		(CC)		Past	260			0.94 (0.60, 1.46)	0.66
				Current	529			0.91 (0.58, 1.43)	0.46
Meta-analysis ² [5,8,26]			Both	All	1605	Diet	-	1.06 (0.88, 1.28)	-
Folate									
Bassett 2012[26]	Australia	Cohort	Both	All	348	Diet	324 µg/day	1.02 (0.69, 1.50)	0.60
				Never	50			1.21 (0.45, 3.27)	0.62

First author, publication year	Country	Study design	Gender	Smoking status	Cases	Measure	Mean/median intake/conc.	Risk estimates ¹	P-trend
Roswall 2010[12]	Denmark	Cohort	Both	Past	143			0.98 (0.56, 1.70)	0.61
				Current	155			1.03 (0.60, 1.77)	0.92
			Both	All	721	Diet	325 µg/day	1.37 (1.01, 1.84)	0.01
				All	721	Supplement	100 µg/day	0.94 (0.69, 1.28)	0.81
Slatore 2008[10]	USA	Cohort	Both	All	521	Supplement	200–399 µg/day ⁴	0.99 (0.79, 1.23)	0.68
				Past 1 ³	226			0.97 (0.70, 1.33)	0.90
				Past 2 ³	93			0.76 (0.44, 1.31)	0.23
				Current	155			1.08 (0.72, 1.62)	0.30
Kabat 2008[8]	Canada	Cohort	Women	All	358	Diet	281 µg/day	1.12 (0.83, 1.52)	0.43
Cho 2006[7] ⁵	North America and Europe	Pooled analysis	Both	All	3155	Diet	184–408 µg/day	0.88 (0.74, 1.04)	0.08
				Never	259			0.69 (0.38, 1.26)	0.23
				Past	981			0.96 (0.78, 1.17)	0.69
				Current	1915			0.86 (0.75, 1.00)	0.06
			Both	All	1734	Diet and	184–496	1.02 (0.83, 1.26)	0.51
				Never	259	supplement	µg/day	1.21 (0.59, 2.45)	0.41
				Past	981			1.00 (0.80, 1.25)	0.38
				Current	1915			1.03 (0.83, 1.27)	0.77

First author, publication year	Country	Study design	Gender	Smoking status	Cases	Measure	Mean/median intake/conc.	Risk estimates ¹	P-trend
Rossi 2006[9]	Australia	Cohort	Men	All	1777	Serum	4.50 µg/L	0.80 (0.58, 1.08)	0.18
			Women	All	1378			0.95 (0.79, 1.13)	0.31
Yuan 2003[11]	Singapore	Cohort	Both	All	482	Diet	149 µg/day	0.82 (0.60, 1.11)	Not reported
				Never	145			0.77 (0.28, 2.10)	0.68
				Past	71			(0.16, 2.93)	Not reported
				Current	268			0.67 (0.31, 1.46)	0.60
Neuhouser 2003[29] ⁶	USA	Cohort	Both	Ever	326	Diet	191–238 µg/day	0.87 (0.61, 1.23)	0.39
Johansson 2010[5]	Europe	Nested CC	Both	All	899	Serum	14.5 nmol/L	0.68 (0.51, 0.90)	<0.001
				Never	96			0.84 (0.43, 1.65)	0.41
				Past	260			0.58 (0.37, 0.91)	0.02
				Current	529			0.54 (0.34, 0.83)	0.003
Ito 2005[31]	Japan	Nested CC	Men	All	163	Serum	5.46 ng/mL	0.82 (0.20, 3.35)	0.95
			Women	All	48		6.63 ng/mL	0.93 (0.10, 8.50)	0.88
Hartman 2001[4]	Finland	Nested CC	Men	Smokers	300	Serum	4.3 ng/mL	0.96 (0.52, 1.79)	0.28
Aune 2011[27]	Uruguay	CC	Both	All	931	Diet	201 µg/day	0.90 (0.58, 1.41)	0.73

First author, publication year	Country	Study design	Gender	Smoking status	Cases	Measure	Mean/median intake/conc.	Risk estimates ¹	P-trend
Shen 2003[3]	USA	CC	Both	Past	470	Diet	179 µg/day	0.53 (0.35, 0.80)	<0.001
Meta-analysis ⁷ [3,7,8,10–12,26–30]		All	Both	All		Diet/ supplement	-	0.94 (0.85, 1.03) $I^2 = 52.0\%$, $P = 0.03$	-
Meta-analysis ⁸ [5,7,11]		All	Both	Never		Diet/serum	-	0.76 (0.50, 1.14) $I^2 < 0.01\%$, $P = 0.91$	-
Meta-analysis ⁷ [7,8,10–12,26,29]		Cohort	Both	All		Diet/ supplement	-	0.97 (0.88, 1.07) $I^2 = 32.0\%$, $P = 0.18$	-
Meta-analysis [3,27]		CC	Both	All		Diet	-	0.68 (0.50, 0.92) $I^2 = 65.8\%$, $P = 0.09$	-
Meta-analysis [4,5,9,31]		All	Both	All		Serum	-	0.76 (0.58, 1.00) $I^2 < 0.01\%$, $P = 0.78$	-

¹ Comparing the highest quantile with the lowest in the study population.

² Risk estimates based on dietary intake, not serum concentrations, were included.

³ Past 1: those who quit smoking 10 years ago; Past 2: those who quit smoking < 10 years ago.

⁴ The range of intakes in the second tertile is shown.

⁵ A pooled analysis of eight prospective studies.

⁶ Risk estimate among placebo arm and the range of intakes in the third quintile are shown.

⁷ Risk estimates based on dietary or supplement intakes (dietary intake was used when both intakes were reported separately), not serum concentrations, were included.

⁸ Risk estimates based on dietary intake and serum concentrations among never smokers were included.