



Association between dietary sodium, potassium intake and lung cancer risk: evidence from the prostate, lung, colorectal and ovarian cancer screening trial and the Women's Health Initiative

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Background: Epidemiological studies have reported that dietary mineral intake plays an important role on lung cancer risk, but the association of sodium, potassium intake is still unclear.

Methods: We determined the association between dietary sodium, potassium intake and lung cancer risk based on the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial and the Women's Health Initiative (WHI). Totally 165,409 participants who completed the baseline questionnaire (BQ) and diet history questionnaire (DHQ) were included into the analytical dataset, including 92,984 (44,959 men and 48,025 women) from the PLCO trial and 72,425 (women only) from the WHI cohort. Multivariable Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) of incident lung cancer associated with dietary potassium and sodium intake. The dose-response relationship was also described using the spline smoothed curve after adjusting covariates.

Results: After the median follow-up of 8.55 and 18.56 years, 1,278 and 1,631 new cases of lung cancer were identified in the PLCO trial and WHI cohort, respectively. Intake of sodium was significantly associated with the incidence of lung cancer in the PLCO trial after multivariate adjustment for men (HR: 1.19, 95% CI: 1.05–1.35; P for linear trend =0.044). There was a suggestion that lung cancer risk had a quadratic curve correlation with the increase of potassium intake for women (third vs. lowest quintile: HR: 0.72, 95% CI: 0.54–0.96; P for quadratic trend =0.042). The similar results showing an inverse association between potassium intake and lung cancer risk were also observed in the WHI cohort for women (highest vs. lowest quintile: HR: 0.82, 95% CI: 0.70–0.97; P for linear trend =0.009).

Conclusions: Appropriate intake of potassium has a protective effect against lung cancer, while high consumption of sodium is associated with an increased risk of lung cancer.

Keywords: Lung cancer; sodium; potassium; cancer screening; Women's Health Initiative

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Introduction

Lung cancer is the most frequent malignant cancer and the leading cause of cancer mortality worldwide (1), with 2.1 million new cases accounting for 11.6% of the total new cancer cases and 1.8 million deaths accounting for 18.4% of the total cancer deaths predicted in 2018 (2). Previous studies have identified the risk factors contributing to the occurrence of lung cancer, such as cigarette smoking, gender and air pollution (3).

Recently, emerging evidence has suggested that intake of dietary minerals may have an impact on the incidence of lung cancer. It was found that both a higher zinc and iron intake was associated with a reduced risk of lung cancer (4,5). Similar protective effects of zinc were also reported in three large case-control studies. For the association between calcium intake and lung cancer risk, however, the findings were inconsistent. An increased risk of lung cancer risk on calcium intake was identified in a case-control study by Zhou *et al.*, while an inverse association was found in the National Cancer Institute (NIH)-American Association of Retired Persons Diet and Health study (6). Moreover, several studies also showed that both copper and selenium may decrease the risk of lung cancer (7).

Potassium and sodium are two of the necessary trace elements in the human body, which are mainly derived from diet. Previously, several studies reported that high intake of potassium was negatively related to the occurrence of colorectal cancer, and high sodium consumption could increase the risk of renal cell cancer, colorectal cancer, and gastric cancer (8-11). However, there are few studies on the relationship between potassium, sodium intake and the risk of lung cancer.

In the present study, we aimed to evaluate whether dietary potassium, sodium intake was associated with lung cancer risk using the data from both the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial and the observational study of the Women's Health Initiative (WHI).

The authors present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/tlcr-20-870>).

Methods

Study population

Totally 111,383 out of 154,897 participants in the PLCO

cancer screening trial conducted at 10 study centers and sponsored by the National Cancer Institute (NCI) which was carried out to evaluate whether selected screening methods could reduce the mortality from prostate, lung, colorectal, and ovarian cancer completed the baseline questionnaire (BQ) and diet history questionnaire (DHQ) (12). After excluding 7 deaths prior to completion of the DHQ, 16 cases without the completion date of the DHQ, 3,039 cases skipping ≥ 8 food frequency questions and 2,179 cases of extreme energy intake, there were 106,435 participants completing the eligible DHQ. Finally 92,984 cases were included into the analytical dataset after excluding 4,354 deaths or cancer cases diagnosed prior to the date of DHQ and 9,097 cases of missing necessary covariates (alcohol intake, smoking status, pack-years of smoking, body mass index (BMI), education, diabetes history, and family history of lung cancer) (13). The flow diagram describing the population selection process was listed in *Figure 1A*.

A total of 93,676 postmenopausal females aged 50-79 years were enrolled in the observational study (a sub-cohort) of the WHI which was a long-term national health study sponsored by the National Heart, Lung, and Blood Institute (NHLBI), with the purpose of exploring new risk indicators and biomarkers of morbidity and mortality in postmenopausal females (14). A similar selection procedure was performed in the WHI cohort (*Figure 1B*). Finally, 165,409 participants were included into the overall analytical dataset, including 92,984 (44,959 males and 48,025 females) from the PLCO trial and 72,425 (females only) from the WHI cohort.

The studies were approved by the corresponding institutional review boards and all the participants provided written informed consent (12,15).

Data collection

In the PLCO trial, all the participants completed a self-administered baseline questionnaire with demographic information, such as age, gender, race, education, family history of cancer, smoking history, medical history, and past screenings. BMI was computed as weight (kg)/height (m)². Dietary data were collected through Dietary History Questionnaire (DHQ) which included 156 questions about the consumption frequencies of various foods, drinks, supplements, and other items. Furthermore, the daily intake of nutrients including potassium and sodium was derived from the frequency and portion-size responses to the food frequency questionnaire (FFQ), in which the

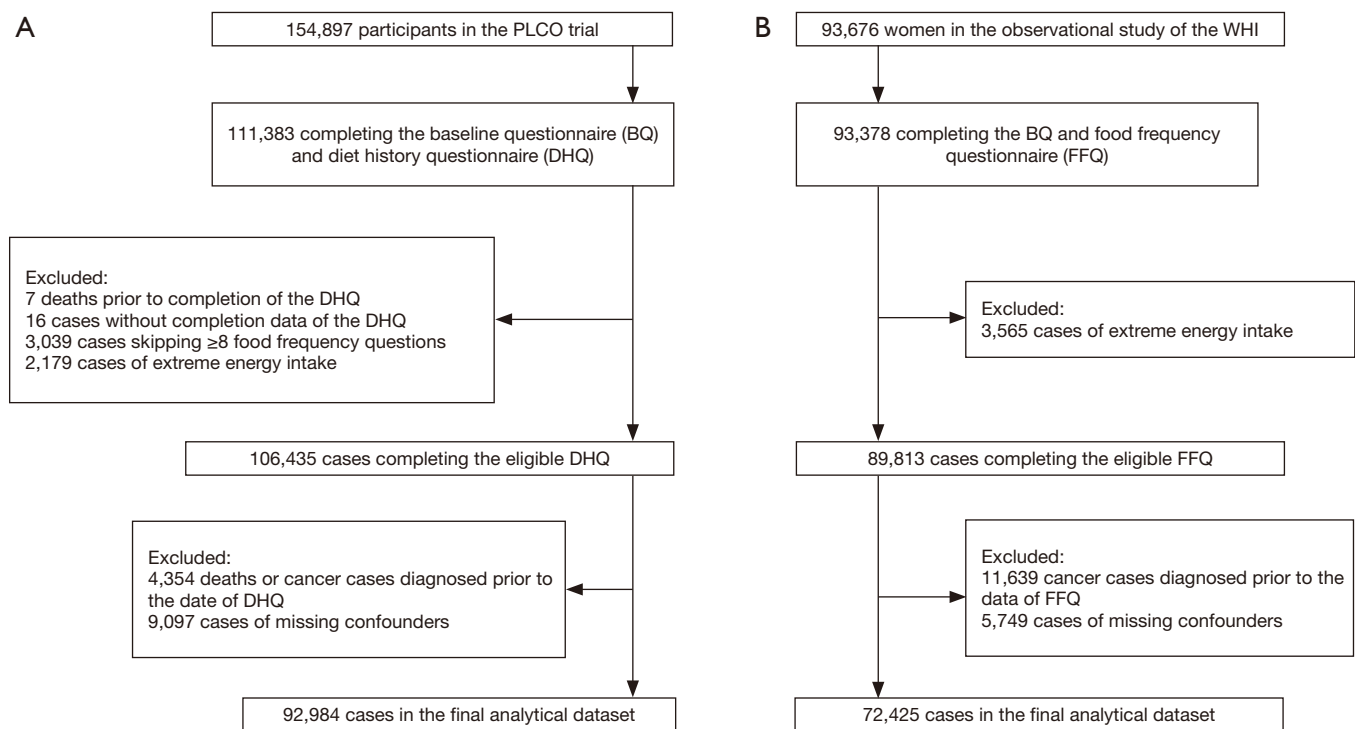


Figure 1 The flow diagram describing the population selection process: the PLCO trial (A) and the observational study of the WHI (B).

relevant nutrient values were multiplied by the frequency and summed across. The nutrient composition databases were calculated by DietCalc software, in conjunction with a nutrient database based on the national dietary data [USDA's 1994–96 Continuing Survey of Food Intakes by Individuals (CSFII), available from the USDA Food Survey Research Group, or the Nutrition Data Systems for Research (NDS-R) from the University of Minnesota] (16).

The demographic information was collected for every participant in the WHI cohort. Dietary data were collected through FFQ with 145 items which consisted of three basic components: a food list, a frequency response section for subjects to report how often each food was eaten and portion-size information. Additionally, the nutrient database used in the FFQ analysis software was based on the University of Minnesota's Nutrition Coordinating Center's (UM-NCC) nutrient database.

Confirmation of lung cancer

In both cohorts, the reports of lung cancer were collected through various methods including but not limited to the annual questionnaires which were mailed to all participants to determine the incidence of lung cancer and the

diagnostic data within one year, family reports and death certificates. All the reports of lung cancer diagnosis were followed up and confirmed through abstraction of medical records (12,15).

Statistical analysis

When analyzing the association between dietary sodium, potassium intake and lung cancer risk, the mineral intake was firstly energy-adjusted by the residual method (17). For the primary analysis, participants were divided into quintiles of average intake of sodium or potassium in each cohort. The associations between mineral intake and risk of incidence were analyzed separately for different genders as the overall dietary mineral intake were significantly different between male and female. In addition, a pooled analysis was performed on all the females from the two cohorts.

Multivariable Cox proportional hazards regression was used to calculate the hazard ratios (HR) and its 95% confidence intervals (CI) for incident lung cancer associated with dietary potassium and sodium intake. Follow-up time was defined as the interval between the recruitment date to that of lung cancer diagnosis or withdrawal (death or the end of follow-up). Covariates adjusted in the Cox model

included age, gender, BMI at baseline, energy from diet, education level (low: high school or below, intermediate: post high school or junior college, high: college or above), alcohol consumption, smoking status (never smokers, former smokers <20 pack-years, former smokers \geq 20 pack-years, current smokers <20 pack-years, current smokers \geq 20 pack-years), previous history of diabetes mellitus, and family history of lung cancer. The family history of cancer, but not lung cancer, was adjusted in the multivariable regression model for the WHI cohort because the information of lung cancer was not collected. When testing for trend across quintiles of mineral intake, median values were assigned to denote the corresponding quintiles. Furthermore, the dose-response relationship between dietary sodium or potassium intake and the lung cancer risk was described in a Cox proportional hazard model using the spline smoothed curve after adjusting covariates mentioned previously (18).

We further performed extensive sensitivity analysis to evaluate the robustness of our findings. Some studies suggested that yogurt rich in potassium was inversely associated with lung cancer risk after adjustment for other risk factors (19). In our study, it was found the average yogurt intake of females was twice as much as that of males in the PLCO trial. Besides, the ethnic differences may also have an impact on the results. Therefore, sensitivity analyses were conducted by including yogurt intake or race in the multivariable model. In order to reduce the bias due to measurement errors, we applied the “calibration” equations, details of the study have been described in (20), to FFQ data to estimate calibrated intake and performed the same Cox proportional hazards regression as another sensitivity analysis for the WHI cohort.

Additional analysis was performed after excluding the participants who were diagnosed with cancers other than lung cancer. We also evaluate the association between potassium and sodium intake and lung cancer risk at the different stratum determined by smoking status and classification [non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC)].

All statistical analyses were performed using R software (version 3.5.1). A value of $P \leq 0.05$ was considered statistically significant.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The usage of the lung cancer database in the PLCO and WHI studies was

authorized by the ethics committees of the data providers and Nanjing Medical University.

Results

Description of the study population

Table 1 showed the baseline characteristics of lung cancer cases and controls in the PLCO trial and WHI cohort. After the median follow-up of 8.55 and 18.56 years, 1,278 and 1,631 new cases of lung cancer were identified in the PLCO trial and WHI cohort, respectively. Significant differences were exhibited between confirmed and non-confirmed lung cancer cases in the PLCO trial and WHI cohort regarding age, BMI, educational level, smoking status, alcohol consumption and family history of cancer ($P < 0.05$). The cases in the PLCO trial were more likely to be male ($P < 0.001$) and had a higher total energy intake ($P = 0.005$), while those in the WHI cohort had a lower intake of potassium ($P = 0.001$). Baseline characteristics of the study population according to quintiles of mineral intake and the correlation coefficients between minerals and dietary food sources were described in Tables S1-S3. It is important to notice that the distributions of mineral intake were significantly different between male and female. Males in the PLCO cohorts had higher sodium and potassium intakes than females in both the PLCO and WHI cohorts ($P < 0.001$), which highlight the importance of making gender-specific analysis on the lung cancer risk on dietary mineral intakes (Figure S1).

Gender-specific association between mineral intake and risk of lung cancer

As shown in Table 2, higher intake of potassium was associated with a decreased risk of lung cancer in the WHI cohort. Compared with the subgroup with the lowest potassium intake (median intake 1,914 mg/day), the HRs and 95% CIs for subgroups with the second highest (median intake 2,935 mg/day) and highest intake (median intake 3,450 mg/day) were 0.85 (0.73, 0.99) and 0.82 (0.70, 0.97). We also identified a significant linear trend between potassium intake and lung cancer risk ($P = 0.009$). Furthermore, the spline smoothed curve analysis demonstrated a significant dose-response association between potassium intake and risk of incident lung cancer (Figure 2A). For females in the PLCO trial, although not significant, higher potassium intake groups

Table 1 Baseline characteristics of lung cancer cases and controls in the PLCO trial and the WHI cohort

Baseline characteristics (mean ± SD)	The PLCO trial			The WHI cohort		
	Confirmed LC	Non-confirmed LC	P value ^b	Confirmed LC	Non-confirmed LC	P value ^b
Total (N)	1,278	91,706		1,631	70,794	
Potassium intake (g/day) ^a	3.25±0.83	3.26±0.76	0.965	2.62±0.63	2.66±0.64	0.001
Sodium intake (g/day) ^a	2.71±0.70	2.74±0.56	0.171	2.65±0.49	2.64±0.49	0.349
Age (year)	64.04±5.15	62.30±5.26	<0.001	64.89±6.72	63.34±7.33	<0.001
Gender (%)						
Female	42.5	51.8	<0.001	100	100	
Male	57.5	48.2		–	–	
Body mass index (kg/m ²)	26.57±4.37	27.27±4.81	<0.001	26.66±5.47	27.19±5.82	<0.001
Education (%)						
Low	35.4	28.6	<0.001	20.3	20.9	0.041
Middle	40.4	34.4		39.2	36.2	
High	24.2	37.0		40.5	42.9	
Cigarette smoking (%)						
Never	8.2	48.4	<0.001	18.3	53.1	<0.001
Former <20 pack-years	6.7	18.8		17.3	27.0	
Former ≥20 pack-years	44.5	24.0		39.6	14.1	
Current <20 pack-years	1.1	0.8		4.4	2.4	
Current ≥20 pack-years	39.5	8.0		20.4	3.4	
Alcohol intake (g/day)	14.76±37.39	9.72±25.40	<0.001	7.63±12.92	5.53±11.10	<0.001
Energy intake (kcal/day)	1,815.8±800.3	1,740.0±733.1	0.005	1,569.1±576.8	1,570.0±596.2	0.636
Diabetes (%)	7.12	6.51	0.408	5.15	5.24	0.910
Family history of lung cancer (%)	18.78	10.59	<0.001			
Family history of cancer (%)	60.5	54.7	<0.001	67.87	63.99	0.001

SD, standard deviation; LC, lung cancer. ^a, intake was energy-adjusted. ^b, P value for difference was tested using Wilcoxon rank sum test (continuous) or Chi-square test (categorical).

showed protective effects against lung cancer. As the spline smoothed curve shown in *Figure 2B*, the trend of HRs with potassium intake were in quadratic, subgroup with median potassium intake was associated with 26% reduction in the risk of lung cancer (compared with the lowest: HR: 0.72, 95% CI: 0.54–0.96). This was verified by fitting a quadratic regression with a squared term of potassium intake (P for quadratic trend =0.04). Similar trend was also observed in the pooled analysis (*Figure 2C*). However, the association was not significant for potassium intake in males (HR: 1.06, 95% CI: 0.97–1.17, *Figure 2D*).

As for sodium intake, higher sodium intake was

significantly associated with increased lung cancer risk for males in the PLCO trial (HR: 1.19, 95% CI: 1.05–1.35, P for linear trend =0.044). For females, we observed a linear trend for sodium intake against lung cancer in the PLCO (P for trend =0.022), while only a suggestive but not significant association in the WHI cohort (HR: 1.10, 95% CI: 0.99–1.21; P for trend =0.080). Corresponding spline smoothed curves were shown in *Figure 3*.

Pooled analysis on females in both cohorts

A pooled analysis was performed by combining females

Table 2 Gender-specific hazard ratios and 95% confidence intervals of lung cancer based on categories of dietary mineral intake

	Continuous	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Potassium						
WHI (female only)						
Dietary intake ^a	2,619.5	<2,153.6	2,153.6–2,473.8	2,473.8–2,768.2	2,768.2–3,139.5	≥3,139.5
Cases/person-years	1,631/1,123,470	368/207,916	336/220,409	332/228,708	304/231,972	291/234,465
Multivariable model HR ^b	0.94 (0.87, 1.02)	1.00	0.93 (0.80, 1.08)	0.92 (0.79, 1.07)	0.85 (0.73, 0.99)	0.82 (0.70, 0.97)
P value	0.124			P _{trend} ^c =0.009		
Female in the PLCO						
Dietary intake ^a	2,943.8	<2,463.4	2,463.4–2,797.0	2,797.0–3,096.8	3,096.8–3,487.7	≥3,487.7
Cases/person-years	543/390,992	123/77,876	106/77,994	87/77,975	103/78,589	124/78,558
Multivariable model HR ^b	0.96 (0.85, 1.09)	1.00	0.90 (0.69, 1.17)	0.72 (0.54, 0.96)	0.83 (0.63, 1.09)	0.92 (0.72, 1.19)
P value	0.546			P _{trend} ^c =0.553		
Male in the PLCO						
Dietary intake ^a	3,489.9	<2,935.9	2,935.9–3,319.7	3,319.7–3,670.0	3,670.0–4,142.0	≥4,142.0
Cases/person-years	735/343,836	152/68,795	127/68,496	145/68,642	159/68,905	152/68,998
Multivariable model HR ^b	1.06 (0.97, 1.17)	1.00	0.93 (0.73, 1.18)	1.05 (0.83, 1.33)	1.12 (0.89, 1.41)	1.05 (0.83, 1.33)
P value	0.188			P _{trend} ^c =0.348		
Sodium						
WHI (female only)						
Dietary intake ^a	2,620.2	<2,291.5	2,291.5–2,522.5	2,522.5–2,722.4	2,722.4–2,980.3	≥2,980.3
Cases/person-years	1,631/1,123,470	337/221,914	293/224,463	343/224,825	313/226,959	345/225,309
Multivariable model HR ^b	1.10 (0.99, 1.21)	1.00	0.94 (0.80, 1.11)	1.15 (0.99, 1.35)	1.05 (0.90, 1.23)	1.12 (0.96, 1.30)
P value	0.074			P _{trend} ^c =0.080		
Female in the PLCO						
Dietary intake ^a	2,361.2	<2,083.6	2,083.6–2,280.3	2,280.3–2,442.9	2,442.9–2,656.4	≥2,656.4
Cases/person-years	543/390,992	143/77,508	101/78,109	106/78,154	100/78,802	93/78,418
Multivariable model HR ^b	0.83 (0.68, 1.01)	1.00	0.80 (0.62, 1.04)	0.91 (0.70, 1.18)	0.82 (0.63, 1.07)	0.71 (0.54, 0.93)
P value	0.057			P _{trend} ^c =0.022		
Male in the PLCO						
Dietary intake ^a	3,108.9	<2,732.1	2,732.1–2,996.7	2,996.7–3,229.6	3,229.6–3,551.6	≥3551.6
Cases/person-years	735/343,836	155/68,264	127/68,502	149/68,646	159/69,025	145/69,399
Multivariable model HR ^b	1.19 (1.05, 1.35)	1.00	1.00 (0.78, 1.28)	1.24 (0.97, 1.57)	1.33 (1.05, 1.68)	1.19 (0.93, 1.53)
P value	0.008			P _{trend} ^c =0.044		

^a, mineral intake was energy-adjusted (mg/day), median intake for continuous and range for quintiles. ^b, Cox proportional hazard models were used to adjust age, body mass index (kg/m²), energy intake (kcal/day), educational level (3 categories), alcohol consumption (g/day), smoking status (never smokers, former smokers <20 pack-years, former smokers ≥20 pack-years, current smokers <20 pack-years, current smokers ≥20 pack-years), history of diabetes (yes or no), and family history of lung cancer (yes or no) for the PLCO trial or family history of cancer (yes or no) for the WHI cohort. ^c, test for linear trend was estimated by assigning the median value of sodium or potassium intake in each quintile.

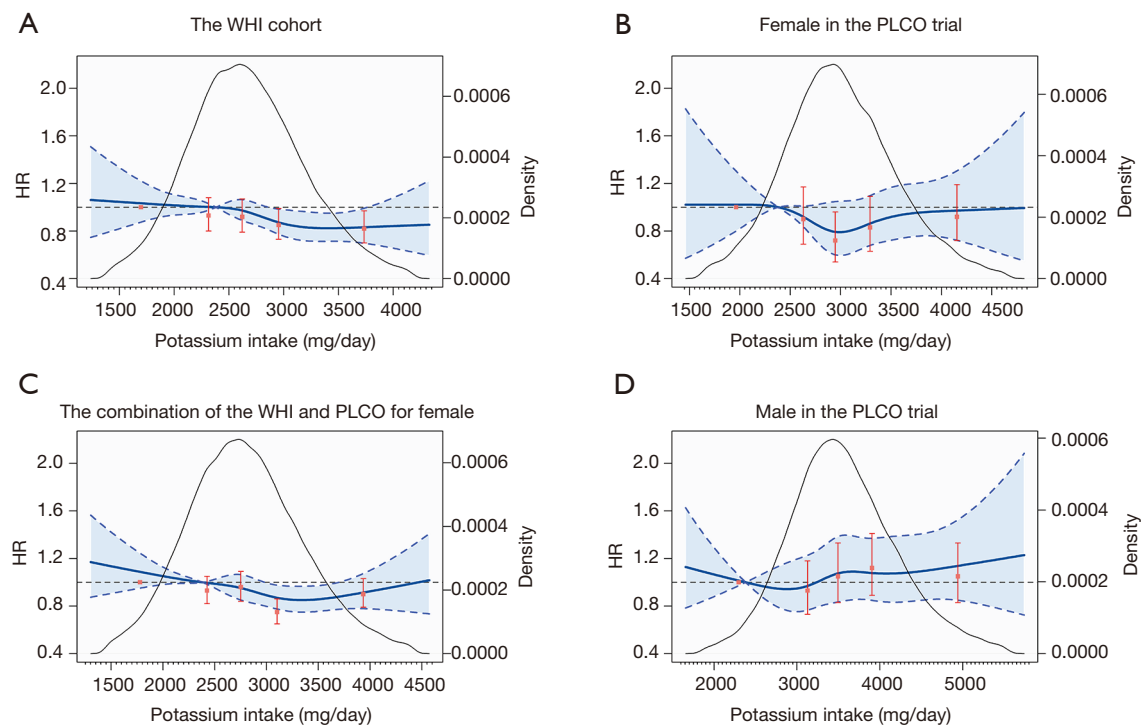


Figure 2 Dose-response association between dietary potassium intake (energy-adjusted) and lung cancer risk for females in the WHI cohort (A), females in the PLCO trial (B), the combination of females (C), and males in the PLCO trial (D) using spline smoothed model. Multivariable risk estimate was calculated to adjust all covariates by spline regression with three knots (20th percentiles as the reference, 2,381 mg/day). Blue solid line represented point estimates, dashed lines and shadow area represented 95% confidence intervals. Red solid points and vertical lines represented HRs and 95% CIs of lung cancer based on categories of dietary potassium intake (compared with the lowest quintile), respectively. Black curve showed the kernel density estimates of participants (right y-axis) consuming of potassium.

in both cohorts. Participants were divided based on the quintiles of mineral intakes in the combined population. The results suggested a quadric relationship between potassium intake and lung cancer risk (Figure 2C). The HR with the second highest (median intake 3,079 mg/day) versus the lowest quintiles (median intake 1,998 mg/day) of potassium intake was 0.75 (95% CI: 0.65–0.86), but with no significant difference for the highest quintile (HR: 0.90, 95% CI: 0.79–1.03) (Table 3). As for sodium intake, although the association was not significant (HR: 1.03, 95% CI: 0.94–1.13), an upward trend was observed at the end of the spline curve (Figure 3C).

Results from the sensitivity analysis

After additional adjustment for yogurt intake and race, the results were basically consistent with the above (Tables S4,S5). In the sensitivity analysis using calibrated potassium and sodium intake, consistent dose-response

relationship was observed in the WHI cohort (data not shown). Besides, we observed that stratified analyses by smoking status or cancer type showed consistent results with the main analysis, although the association is not significant for SCLC patients due to limited sample size (Tables S6–S9).

Discussion

To the best of our knowledge, this was the first study to investigate the association between dietary sodium and potassium intake and lung cancer risk. Based on two prospective cohort studies, the association between mineral intake and lung cancer risk was analyzed systematically in our study. The main findings suggested that appropriate intake of potassium was associated with a reduced risk of lung cancer, but once excessive, the protective effect would be weakened. High-level intake of sodium was related to a higher risk of lung cancer for males. However, no significant

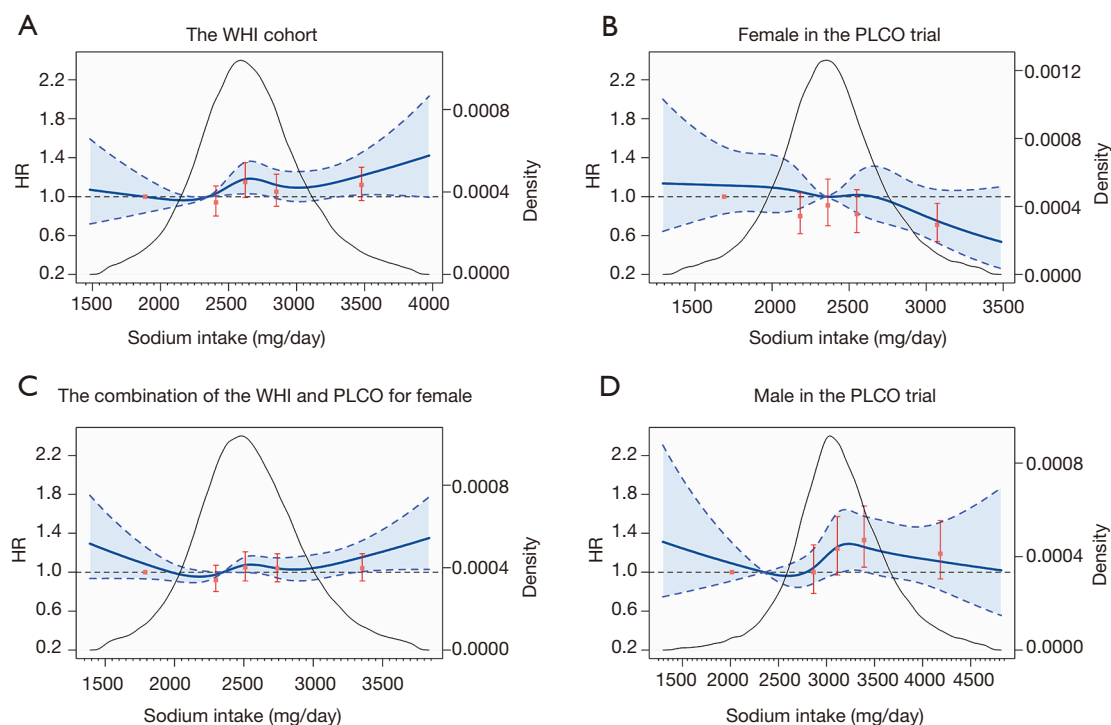


Figure 3 Dose-response association between dietary sodium intake (energy-adjusted) and lung cancer risk for females in the WHI cohort (A), females in the PLCO trial (B), the combination of females (C), and males in the PLCO trial (D) using spline smoothed model. Multivariable risk estimate was calculated to adjust all covariates by spline regression with three knots (20th percentiles as the reference, 2,349 mg/day). Blue solid line represented point estimates, dashed lines and shadow area represented 95% confidence intervals. Red solid points and vertical lines represented HRs and 95% CIs of lung cancer based on categories of dietary sodium intake (compared with the lowest quintile), respectively. Black curve showed the kernel density estimates of participants (right y-axis) consuming of sodium.

correlation was observed for females due to the low overall consumption of sodium.

Principal findings and biological rationale

In the present study, a protective effect against lung cancer risk was observed in females with appropriate high-level intake of potassium in both cohorts. As the spline regression plots shown, the HRs had a quadratic curve correlation with the increase of potassium intake in the PLCO trial, but a linear downward trend in the WHI cohort. A possible explanation for different patterns in the two cohorts maybe related to different levels of potassium intake. Additionally, the median intake for females in the WHI cohort was less than that in the PLCO trial. Thus, the ascending part of the curve could possibly be unobserved due to lack of participants with high-level consumption of potassium.

Emerging evidence suggests that the necrosis of tumor cells can release an intracellular ion and potassium

into extracellular fluid. The increased concentration of extracellular potassium leads to increased intracellular potassium within T-cells, which acts to impair T-cells receptor (TCR)-driven Akt-mTOR phosphorylation and effector programs. This can cause a profound suppression of T-cells effector function (21,22). T-cells can recognize the neoantigens, generated by the tumor cells, and then target and kill the cells that may be cancerous. In addition, T-cells also produce chemicals to help regulate the immune response and protect against tumors (23). Lacking of potassium intake is associated with the lower lung function (24). And there are evidences suggesting that potatoes, tomatoes, bananas and yogurt which are all rich in potassium can reduce the incidence of lung cancer effectively (25,26). In combination with the above-mentioned studies, our results indicated that appropriately increasing potassium intake could strengthen the lung function and decrease the incidence of lung cancer. However, once potassium intake exceeded the daily requirement, the concentration

Table 3 Hazard ratios and 95% confidence intervals of lung cancer based on categories of dietary potassium intake for female

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P _{trend} ^c
Dietary potassium intake ^a	<2,253.6	2,253.6–2,597.5	2,597.5–2,906.6	2,906.6–3,297.8	≥3,297.8	
PLCO (N=48,025)						
Cases/person-years	78/44,846	80/60,993	108/78,777	106/93,023	171/113,353	
Multivariable model HR ^b	1.00	0.87 (0.63, 1.19)	0.87 (0.65, 1.18)	0.71 (0.53, 0.97)	0.87 (0.66, 1.15)	0.359
WHI (N=72,425)						
Cases/person-years	461/269,115	379/256,249	342/228,387	230/204,040	219/165,679	
Multivariable model HR ^b	1.00	0.94 (0.82, 1.08)	0.98 (0.85, 1.13)	0.75 (0.64, 0.89)	0.90 (0.76, 1.06)	0.023
ALL (N=120,450)						
Cases/person-years	539/313,961	459/317,242	450/307,165	336/297,063	390/279,032	
Multivariable model HR ^b	1.00	0.93 (0.82, 1.05)	0.96 (0.84, 1.09)	0.75 (0.65, 0.86)	0.90 (0.79, 1.03)	0.017
Dietary sodium intake ^a	<2,186.3	2,186.3–2,409.5	2,409.5–2,610.6	2,610.6–2,871.8	≥2,871.8	
PLCO (N=48,025)						
Cases/person-years	184/114,533	141/103,569	101/80,981	75/55,696	42/36,213	
Multivariable model HR ^b	1.00	1.01 (0.81, 1.27)	0.93 (0.72, 1.19)	0.95 (0.72, 1.25)	0.76 (0.54, 1.07)	0.150
WHI (N=72,425)						
Cases/person-years	234/151,282	222/175,731	333/220,300	387/269,553	455/306,604	
Multivariable model HR ^b	1.00	0.91 (0.75, 1.09)	1.14 (0.96, 1.36)	1.10 (0.93, 1.30)	1.12 (0.95, 1.32)	0.05
ALL (N=120,450)						
Cases/person-years	418/265,815	363/279,300	434/301,281	462/325,249	497/342,817	
Multivariable model HR ^b	1.00	0.92 (0.80, 1.07)	1.05 (0.91, 1.21)	1.04 (0.90, 1.19)	1.04 (0.91, 1.19)	0.284

^a, mineral intake was energy-adjusted (mg/day), median intake for continuous and range for quintiles. ^b, Cox proportional hazard models were used to adjust age, body mass index (kg/m²), energy intake (kcal/day), educational level (3 categories), alcohol consumption (g/day), smoking status (never smokers, former smokers <20 pack-years, former smokers ≥20 pack-years, current smokers <20 pack-years, current smokers ≥20 pack-years), history of diabetes (yes or no), and family history of cancer (yes or no). ^c, test for linear trend was estimated by assigning the median value of potassium intake in each quintile.

of potassium in microenvironment would increase, which could suppress the activity of T-cells and eventually reduce the protective effect on the occurrence of lung cancer.

The biological mechanisms underlying the association between lung cancer risk and intake of sodium remain unclear. Zhang *et al.* found that high salt intake, a major source of dietary sodium, increased the proinflammatory gene expression of mouse alveolar macrophages and aggravated inflammation in lungs, which was associated with the risk of lung cancer (27). Several cohort studies exhibited that high salt dietary was associated with an increased risk and mortality of lung cancer (28-30). In the present study, an association was found between an increased risk of lung cancer and higher sodium consumption for males in the

PLCO trial and a borderline effect in the WHI cohort. An inconsistent borderline effect was also shown for females in the PLCO trial. It was worth noting that the overall energy-adjusted sodium intake of females in the PLCO trial was less than that of females in the WHI cohort and males in the PLCO trial. And females in the PLCO trial, especially those with higher quintiles, had a high proportion of ibuprofen use, which may contribute to lung cancer prevention (31). In addition, it was plausible that some potential lung cancer patients may not be diagnosed due to the shorter follow-up time for the PLCO trial than WHI cohort, with the median follow-up of 8.55 and 18.56 years respectively.

To date, a growing number of studies show the role of

dietary mineral intake in the development of cancer. For instance, copper and magnesium can maintain the integrity of DNA by preventing oxidative DNA damage (32,33). Calcium plays an important role in the processes of cell proliferation and carcinogenesis by affecting the cell cycle regulation (34). Minerals participate in various processes of DNA repair, RNA expression, protein synthesis, immune function and so on (21,35-37). In the present study, sodium and potassium, two of the most important minerals in diet, was shown to involve in the cancer genesis.

Lacking of potassium intake and excessive intake of sodium can elevate the blood pressure and the risk of cardiovascular disease, stroke and coronary heart disease (38). A recent study has shown that replacement of regular salt with potassium-enriched substitutes is conducive to reducing the blood pressure (39). The World Health Organization suggests a potassium intake of at least 3,510 mg per day and a reduction of sodium to less than 2,000 mg per day for adults (40). These all recommend a healthy dietary pattern of high potassium and low sodium, further verifying the reliability of our conclusion.

Strengths and limitations of this study

There were several strengths in our study. First, this study was made based on the PLCO trial and the WHI which were large-scale, prospective, cohort studies with a relative complete follow-up information (41). Secondly, the combination of the two large-scale cohorts provided sufficient power to detect the association. Nevertheless, several limitations needed to be noted, including only description of the dietary baseline information, possible residual confounding or confounding by unmeasured factors, and the accuracy of dietary intake measurement.

Conclusions

Our results suggest that appropriate consumption of potassium has a protective effect against lung cancer; high consumption of sodium is related to an increased risk of lung cancer, along with the presence of a dose-response relationship despite the modest magnitude of estimate.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tlcr-20-870>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The usage of the lung cancer database in the PLCO and WHI studies was authorized by the ethics committees of the data providers and Nanjing Medical University.

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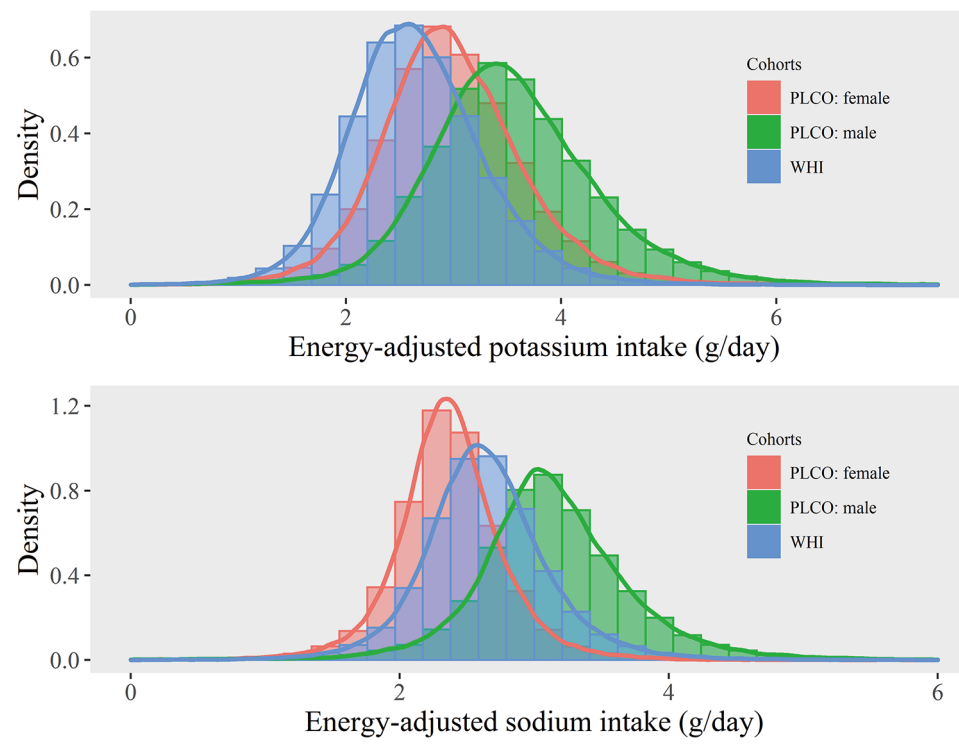


Figure S1 The distributions of potassium and sodium intake in the PLCO and WHI cohorts. Solid lines represented kernel density estimates.

Table S1 Baseline characteristics of the study population in the PLCO trial based on quintiles of sodium and potassium intake

Baseline characteristics Quintiles ^a	Sodium						Potassium					
	1 (low)	2	3	4	5 (high)	P value ^d	1 (low)	2	3	4	5 (high)	P value ^d
Total (N)	18597	18597	18597	18597	18596		18597	18597	18597	18597	18596	
No. of lung cancer (n)	299	229	238	265	247		273	243	243	247	272	
Median mineral intake (mg/day) ^b	2201.5	2526.2	2719.2	2932.2	3329.6	<0.001	2410.4	2878.9	3203.5	3567.7	4177.1	<0.001
Age (year) ^c	62.5±5.4	62.6±5.3	62.4±5.3	62.2±5.2	61.9±5.1	<0.001	61.8±5.2	62.3±5.2	62.5±5.3	62.6±5.3	62.5±5.3	<0.001
Gender (%)												
Female	45.8	58.6	58.5	54.6	40.7	<0.001	41.1	52.6	55.3	56.1	53.1	<0.001
Male	54.2	41.4	41.5	45.4	59.3		58.9	47.4	44.7	43.9	46.9	
Body mass index (kg/m ²) ^c	26.6±4.5	26.7±4.6	27.1±4.7	27.6±4.9	28.3±5.1	<0.001	27.7±4.9	27.4±4.8	27.2±4.8	27.0±4.7	27.0±4.7	<0.001
Education (%)												
Low	28.9	29.3	28.6	28.2	28.3	0.100	32.6	29.5	28.2	27.0	26.0	<0.001
Middle	34.8	34.5	34.4	34.7	34.0		34.5	34.9	34.7	34.3	34.0	
High	36.3	36.2	37.0	37.1	37.7		32.9	35.6	37.1	38.7	40.0	
Cigarette smoking (%)												
Never	44.9	51.2	51.1	48.5	43.6	<0.001	47.2	49.8	49.2	48.0	45.2	<0.001
Former <20 pack-years	18.6	18.6	18.9	18.4	18.5		16.7	18.2	19.0	19.4	19.7	
Former ≥20 pack-years	24.4	21.7	22.1	24.7	28.5		25.1	23.3	23.6	24.0	25.5	
Current <20 pack-years	0.9	0.8	0.7	0.8	0.8		0.9	0.8	0.7	0.8	0.8	
Current ≥20 pack-years	11.2	7.7	7.2	7.4	8.6		10.2	7.9	7.5	7.8	8.8	
Alcohol intake (g/day) ^c	23.5±50.4	7.6±12.9	6.1±11.1	5.7±10.1	5.9±10.6	<0.001	18.9±48.6	8.5±17.1	7.6±13.9	7.2±13.1	6.7±12.3	<0.001
Energy intake (kcal/day) ^c	1951±831	1506±620	1507±607	1652±618	2088±766	<0.001	1928±899	1585±678	1587±634	1664±629	1940±708	<0.001
Diabetes (%)	3.3	4.3	5.8	7.7	11.5	<0.001	5.7	6.6	6.5	6.7	7.1	<0.001
Family history of lung cancer (%)	11.0	10.6	10.3	10.6	11.1	0.090	10.4	10.5	11.0	11.0	10.6	0.153

^a, quintile boundaries were based on sub-cohort members. ^b, intake was energy-adjusted (mg/day). ^c, all values were mean ± sd. ^d, P value for difference was tested using Kruskal-Wallis test (continuous) or Chi-square test (categorical).

Table S2 Baseline characteristics of the study population in the WHI cohort based on quintiles of sodium and potassium intake

Baseline characteristics Quintiles ^a	Sodium						Potassium					
	1 (low)	2	3	4	5 (high)	P value ^d	1 (low)	2	3	4	5 (high)	P value ^d
Total (N)	14485	14485	14485	14485	14485		14485	14485	14485	14485	14485	
No. of lung cancer (n)	337	293	343	313	345		368	336	332	304	291	
Median mineral intake (mg/day) ^b	2100.8	2416.7	2620.2	2835.3	3212.1	<0.001	1914.1	2324.2	2619.5	2934.5	3450.3	<0.001
Age (year) ^c	63.1±7.4	63.5±7.3	63.5±7.3	63.4±7.3	63.3±7.2	<0.001	62.2±7.3	63.2±7.4	63.5±7.2	63.8±7.3	64.2±7.2	<0.001
Body mass index (kg/m ²) ^c	27.1±5.9	26.8±5.6	27.0±5.6	27.3±5.8	27.8±6.1	<0.001	28.9±6.7	27.3±5.8	26.8±5.5	26.6±5.4	26.3±5.2	<0.001
Education (%)												
Low	22.7	21.8	21.0	19.9	19.0	<0.001	32.1	23.3	19.1	16.4	13.5	<0.001
Middle	36.8	36.6	36.6	35.6	35.5		38.2	38.0	36.5	35.4	33.2	
High	40.5	41.6	42.4	44.5	45.5		29.7	38.7	44.4	48.2	53.3	
Cigarette smoking (%)												
Never	50.6	53.5	54.0	53.2	50.2	<0.001	51.2	52.3	52.3	52.2	53.5	<0.001
Former <20 pack-years	25.8	26.6	26.7	26.8	28.2		23.5	25.8	27.4	28.9	28.5	
Former ≥20 pack-years	14.8	13.3	13.7	15.0	16.6		14.4	14.9	15.0	14.5	14.6	
Current <20 pack-years	3.0	2.7	2.3	2.0	2.1		3.9	2.9	2.2	1.7	1.4	
Current ≥20 pack-years	5.8	3.9	3.3	3.0	2.9		7.0	4.1	3.1	2.7	2.0	
Alcohol intake (g/day) ^c	9.50±17.9	5.72±10.0	4.68±8.3	4.14±7.6	3.82±7.3	<0.001	5.24±12.7	5.75±11.2	5.91±11.0	5.80±10.5	5.17±10.2	<0.001
Energy intake (kcal/day) ^c	1762±651	1449±524	1420±525	1478±539	1742±631	<0.001	1722±751	1437±563	1452±526	1520±503	1718±534	<0.001
Diabetes (%)	3.3	4.0	4.8	5.8	8.2	<0.001	6.4	5.7	4.7	4.7	4.7	<0.001
Family history of cancer (%)	63.4	64.0	64.7	64.0	64.4	0.171	62.3	63.6	64.5	64.4	65.6	<0.001

^a, quintile boundaries were based on sub-cohort members. ^b, intake was energy-adjusted (mg/day). ^c, all values were mean ± sd. ^d, P value for difference was tested using Kruskal-Wallis test (continuous) or Chi-square test (categorical).

Table S3 Correlation coefficients between dietary mineral intake and dietary food sources

Meals and Nutrients	WHI cohort		PLCO trial	
	Potassium	Sodium	Potassium	Sodium
Fruit	0.574	0.162	0.511	0.178
Vegetable	0.549	0.347	0.663	0.604
Meat or Protein	0.799	0.888	0.515	0.731
Fish and seafood	0.304	0.331	0.292	0.330
Carbohydrate	0.811	0.788	0.814	0.776
Fiber	0.782	0.663	0.791	0.701
Milk	0.605	0.303	0.412	0.207
Yogurt	0.349	0.174	0.163	0.034

All Pearson's correlation coefficients were significantly different from zero (P<0.05).

Table S4 Sensitivity analysis of yogurt intake based on categories of dietary potassium intake in the PLCO trial

	Continuous	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Male (N=44,959)						
Dietary potassium intake ^a	3489.9	<2935.9	2935.9-3319.7	3319.7-3670.0	3670.0-4142.0	≥4142.0
Cases/person-years	735/343836	152/68795	127/68496	145/68642	159/68905	152/68998
Multivariable model HR ^b	1.06 (0.97, 1.17)	1.00	0.93 (0.73, 1.18)	1.05 (0.83, 1.33)	1.12 (0.89, 1.41)	1.05 (0.83, 1.33)
P value	0.191			P _{trend} ^c =0.354		
Female (N=48,025)						
Dietary potassium intake ^a	2943.8	<2463.4	2463.4-2797.0	2797.0-3096.8	3096.8-3487.7	≥3487.7
Cases/person-years	543/390992	123/77876	106/77994	87/77975	103/78589	124/78558
Multivariable model HR ^b	0.97 (0.86, 1.10)	1.00	0.90 (0.69, 1.18)	0.73 (0.55, 0.96)	0.84 (0.64, 1.10)	0.94 (0.72, 1.22)
P value	0.629			P _{trend} ^c =0.633		
ALL (N=92,984)						
Dietary potassium intake ^a	3203.4	<2689.6	2689.6-3044.9	3044.9-3371.5	3371.5-3808.0	≥3808.0
Cases/person-years	1278/734829	273/145886	243/146337	243/146963	247/147928	272/147715
Multivariable model HR ^b	1.03 (0.96, 1.11)	1.00	1.01 (0.85, 1.21)	1.01 (0.85, 1.21)	1.01 (0.84, 1.20)	1.05 (0.88, 1.25)
P value	0.437			P _{trend} ^c =0.607		

^a, potassium intake was energy-adjusted (mg/day), median intake for continuous and range for quintiles. ^b, Cox proportional hazard models were used to adjust age, gender (only in ALL), body mass index (kg/m²), energy intake (kcal/day), educational level (3 categories), alcohol consumption (g/day), yogurt consumption (g/day), smoking status (never smokers, former smokers <20 pack-years, former smokers ≥20 pack-years, current smokers <20 pack-years, current smokers ≥20 pack-years), history of diabetes (yes or no), and family history of lung cancer (yes or no). ^c, test for linear trend was estimated by assigning the median value of potassium intake in each quintile.

Table S5 Sensitivity analysis of race based on categories of dietary mineral intake

	Continuous	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Potassium						
WHI (female only)						
Dietary intake ^a	2619.5	<2153.6	2153.6-2473.8	2473.8-2768.2	2768.2-3139.5	≥3139.5
Cases/person-years	1631/1123470	368/207916	336/220409	332/228708	304/231972	291/234465
Multivariable model HR ^b	0.94 (0.86, 1.02)	1.00	0.93 (0.80, 1.09)	0.92 (0.78, 1.07)	0.84 (0.72, 0.99)	0.82 (0.69, 0.96)
P value	0.112			P _{trend} ^c =0.007		
Female in the PLCO						
Dietary intake ^a	2943.8	<2463.4	2463.4-2797.0	2797.0-3096.8	3096.8-3487.7	≥3487.7
Cases/person-years	543/390992	123/77876	106/77994	87/77975	103/78589	124/78558
Multivariable model HR ^b	0.98 (0.87, 1.11)	1.00	0.92 (0.70, 1.20)	0.73 (0.55, 0.98)	0.85 (0.65, 1.12)	0.95 (0.74, 1.23)
P value	0.725			P _{trend} ^c =0.715		
Male in the PLCO						
Dietary intake ^a	3489.9	<2935.9	2935.9-3319.7	3319.7-3670.0	3670.0-4142.0	≥4142.0
Cases/person-years	735/343836	152/68795	127/68496	145/68642	159/68905	152/68998
Multivariable model HR ^b	1.05 (0.95, 1.15)	1.00	0.90 (0.71, 1.15)	1.01 (0.80, 1.29)	1.07 (0.85, 1.35)	1.01 (0.80, 1.28)
P value	0.346			P _{trend} ^c =0.569		
Sodium						
WHI (female only)						
Dietary intake ^a	2620.2	<2291.5	2291.5-2522.5	2522.5-2722.4	2722.4-2980.3	≥2980.3
Cases/person-years	1631/1123470	337/221914	293/224463	343/224825	313/226959	345/225309
Multivariable model HR ^b	1.09 (0.99, 1.21)	1.00	0.94 (0.80, 1.11)	1.14 (0.98, 1.34)	1.04 (0.89, 1.22)	1.11 (0.95, 1.30)
P value	0.084			P _{trend} ^c =0.093		
Female in the PLCO						
Dietary intake ^a	2361.2	<2083.6	2083.6-2280.3	2280.3-2442.9	2442.9-2656.4	≥2656.4
Cases/person-years	543/390992	143/77508	101/78109	106/78154	100/78802	93/78418
Multivariable model HR ^b	0.86 (0.71, 1.04)	1.00	0.82 (0.63, 1.07)	0.93 (0.72, 1.21)	0.84 (0.65, 1.10)	0.74 (0.56, 0.97)
P value	0.114			P _{trend} ^c =0.043		
Male in the PLCO						
Dietary intake ^a	3108.9	<2732.1	2732.1-2996.7	2996.7-3229.6	3229.6-3551.6	≥3551.6
Cases/person-years	735/343836	155/68264	127/68502	149/68646	159/69025	145/69399
Multivariable model HR ^b	1.18 (1.04, 1.34)	1.00	1.00 (0.78, 1.28)	1.23 (0.97, 1.56)	1.31 (1.04, 1.66)	1.18 (0.92, 1.51)
P value	0.011			P _{trend} ^c =0.055		

^a, mineral intake was energy-adjusted (mg/day), median intake for continuous and range for quintiles. ^b, Cox proportional hazard models were used to adjust age, body mass index (kg/m²), race (white, black, Hispanic, Asian or pacific islander, others), energy intake (kcal/day), educational level (3 categories), alcohol consumption (g/day), smoking status (never smokers, former smokers <20 pack-years, former smokers ≥20 pack-years, current smokers <20 pack-years, current smokers ≥20 pack-years), history of diabetes (yes or no), and family history of lung cancer (yes or no) for the PLCO trial or family history of cancer (yes or no) for the WHI cohort. ^c, test for linear trend was estimated by assigning the median value of sodium or potassium intake in each quintile.

Table S6 Smoking-status-specific hazard ratios and 95% confidence intervals of lung cancer based on categories of dietary sodium intake

	Continuous	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
PLCO (male, N=44,959)						
Non-smoker						
Dietary sodium intake ^a	3083.1	<2728.9	2728.9-2982.2	2982.2-3193.7	3193.7-3486.5	≥3486.5
Cases/person-years	38/132602	7/26494	8/26247	10/26296	10/26764	3/26801
Multivariable model HR ^b	1.00 (0.52, 1.94)	1.00	1.05 (0.37, 2.99)	1.35 (0.49, 3.69)	1.36 (0.50, 3.70)	0.45 (0.11, 1.81)
Smoker						
Dietary sodium intake ^a	3124.7	<2733.5	2733.5-3006.1	3006.1-3251.2	3251.2-3588.8	≥3588.8
Cases/person-years	697/211235	144/41856	125/42163	135/42288	153/42286	140/42642
Multivariable model HR ^b	1.15 (1.01, 1.31)	1.00	0.95 (0.74, 1.22)	1.06 (0.83, 1.36)	1.23 (0.97, 1.57)	1.13 (0.88, 1.46)
PLCO (female, N=48,025)						
Non-smoker						
Dietary sodium intake ^a	2346.0	<2075.4	2075.4-2267.9	2267.9-2423.1	2423.1-2627.2	≥2627.2
Cases/person-years	67/226058	16/45162	12/45091	11/45054	14/45381	14/45370
Multivariable model HR ^b	1.34 (0.77, 2.35)	1.00	0.77 (0.36, 1.65)	0.74 (0.34, 1.62)	0.98 (0.47, 2.05)	1.04 (0.50, 2.16)
Smoker						
Dietary sodium intake ^a	2381.4	<2093.0	2093.0-2297.8	2297.8-2469.7	2469.7-2698.1	≥2698.1
Cases/person-years	476/164935	128/32360	88/33054	97/33042	90/33430	73/33049
Multivariable model HR ^b	0.75 (0.61, 0.93)	1.00	0.7 (0.53, 0.93)	0.8 (0.61, 1.05)	0.77 (0.58, 1.02)	0.63 (0.47, 0.85)
WHI (N=72,425)						
Non-smoker						
Dietary sodium intake ^a	2606.6	<2288.0	2288.0-2512.8	2512.8-2706.5	2706.5-2955.8	≥2955.8
Cases/person-years	299/591252	47/117619	59/118170	75/117939	50/119520	68/118004
Multivariable model HR ^b	1.06 (0.83, 1.36)	1.00	1.18 (0.80, 1.74)	1.48 (1.02, 2.15)	0.96 (0.64, 1.44)	1.31 (0.90, 1.90)
Smoker						
Dietary sodium intake ^a	2635.4	<2294.5	2294.5-2532.3	2532.3-2739.6	2739.6-3008.8	≥3008.8
Cases/person-years	1332/532218	274/104588	247/106122	275/106719	262/107372	274/107417
Multivariable model HR ^b	1.02 (0.91, 1.15)	1.00	0.89 (0.74, 1.06)	1.01 (0.85, 1.19)	0.97 (0.81, 1.15)	1.02 (0.86, 1.21)

^a, mineral intake was energy-adjusted (mg/day), median intake for continuous and range for quintiles. ^b, Cox proportional hazard models were used to adjust age, body mass index (kg/m²), energy intake (kcal/day), educational level (3 categories), alcohol consumption (g/day), history of diabetes (yes or no), and family history of cancer (yes or no).

Table S7 Smoking-status-specific hazard ratios and 95% confidence intervals of lung cancer based on categories of dietary potassium intake

	Continuous	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
PLCO (male, N=44,959)						
Non-smoker						
Dietary potassium intake ^a	3437.7	<2897.7	2897.7-3270.6	3270.6-3601.0	3601.0-4064.8	≥4064.8
Cases/person-years	38/132602	6/26769	9/26261	8/26410	7/26640	8/26522
Multivariable model HR ^b	1.05 (0.67, 1.64)	1.00	1.35 (0.47, 3.85)	1.18 (0.40, 3.47)	1.06 (0.35, 3.20)	1.35 (0.46, 3.96)
Smoker						
Dietary potassium intake ^a	3524.1	<2959.1	2959.1-3350.0	3350.0-3707.1	3707.1-4190.8	≥4190.8
Cases/person-years	697/211235	146/42028	121/42262	141/42213	151/42261	138/42471
Multivariable model HR ^b	1.05 (0.96, 1.16)	1.00	0.87 (0.68, 1.12)	1.01 (0.79, 1.28)	1.09 (0.86, 1.38)	1.01 (0.79, 1.29)
PLCO (female, N=48,025)						
Non-smoker						
Dietary potassium intake ^a	2911.6	<2439.0	2439.0-2767.7	2767.7-3061.8	3061.8-3442.9	≥3442.9
Cases/person-years	67/226058	13/45159	12/45148	8/45041	16/45279	18/45431
Multivariable model HR ^b	1.08 (0.75, 1.55)	1.00	0.84 (0.38, 1.87)	0.54 (0.22, 1.32)	1.06 (0.50, 2.23)	1.18 (0.57, 2.43)
Smoker						
Dietary potassium intake ^a	2987.3	<2497.0	2497.0-2838.6	2838.6-3145.3	3145.3-3547.2	≥3547.2
Cases/person-years	476/164935	113/32702	98/32878	80/32926	86/33252	99/33177
Multivariable model HR ^b	0.89 (0.78, 1.02)	1.00	0.85 (0.64, 1.11)	0.68 (0.51, 0.92)	0.72 (0.54, 0.96)	0.82 (0.63, 1.08)
WHI (N=72,425)						
Non-smoker						
Dietary potassium intake ^a	2620.1	<2155.4	2155.4-2475.3	2475.3-2768.3	2768.3-3141.0	≥3141.0
Cases/person-years	299/591252	49/109249	61/116531	58/120013	56/122309	75/123150
Multivariable model HR ^b	1.02 (0.85, 1.23)	1.00	1.04 (0.71, 1.52)	0.91 (0.61, 1.34)	0.82 (0.55, 1.21)	1.05 (0.72, 1.51)
Smoker						
Dietary potassium intake ^a	2618.2	<2153.2	2153.2-2473.5	2473.5-2768.1	2768.1-3138.1	≥3138.1
Cases/person-years	1332/532218	317/98557	270/103957	278/108909	243/109755	224/111040
Multivariable model HR ^b	0.77 (0.70, 0.85)	1.00	0.77 (0.65, 0.90)	0.74 (0.63, 0.87)	0.63 (0.53, 0.75)	0.57 (0.48, 0.68)

^a, mineral intake was energy-adjusted (mg/day), median intake for continuous and range for quintiles. ^b, Cox proportional hazard models were used to adjust age, body mass index (kg/m²), energy intake (kcal/day), educational level (3 categories), alcohol consumption (g/day), history of diabetes (yes or no), and family history of cancer (yes or no).

Table S8 Hazard ratios and 95% confidence intervals of NSCLC based on categories of dietary mineral intake

	Continuous	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Potassium						
WHI (female only)						
Dietary intake ^a	2620.0	<2154.1	2154.1-2474.5	2474.5-2768.9	2768.9-3139.7	>3139.7
Cases/person-years	1258/1119323	272/207260	248/219708	258/227841	252/231049	228/233465
Multivariable model HR ^b	0.95 (0.87, 1.04)	1.00	0.90 (0.76, 1.08)	0.92 (0.78, 1.10)	0.90 (0.75, 1.07)	0.82 (0.68, 0.98)
P value	0.296			0.044		
Female in the PLCO						
Dietary intake ^a	2943.6	<2463.5	2463.5-2796.9	2796.9-3096.6	3096.6-3487.5	>3487.5
Cases/person-years	466/390602	103/77807	91/77910	76/77886	90/78513	106/78485
Multivariable model HR ^b	0.96 (0.84, 1.09)	1.00	0.90 (0.67, 1.20)	0.73 (0.54, 0.98)	0.84 (0.63, 1.12)	0.92 (0.70, 1.21)
P value	0.504			0.572		
Male in the PLCO						
Dietary intake ^a	3489.3	<2935.4	2935.4-3318.9	3318.9-3669.3	3669.3-4141.1	>4141.1
Cases/person-years	626/343406	129/68713	109/68395	121/68569	138/68812	129/68917
Multivariable model HR ^b	1.06 (0.96, 1.17)	1.00	0.92 (0.71, 1.19)	1.02 (0.79, 1.31)	1.12 (0.88, 1.44)	1.05 (0.81, 1.35)
P value	0.248			0.380		
Female in two cohorts						
Dietary intake ^a	2750.1	<2254.2	2254.2-2598.0	2598.0-2907.1	2907.1-3298.1	>3298.1
Cases/person-years	1724/1509925	401/313186	360/316330	370/306196	276/296119	317/278094
Multivariable model HR ^b	0.95 (0.88, 1.03)	1.00	0.94 (0.82, 1.09)	1.00 (0.87, 1.16)	0.77 (0.66, 0.91)	0.91 (0.78, 1.06)
P value	0.201			0.079		
Sodium						
WHI (female only)						
Dietary intake ^a	2620.1	<2291.5	2291.5-2522.3	2522.3-2722.2	2722.2-2980.2	>2980.2
Cases/person-years	1258/1119323	254/221225	237/223500	264/224031	237/226100	266/224467
Multivariable model HR ^b	1.10 (0.98, 1.23)	1.00	1.00 (0.84, 1.20)	1.16 (0.97, 1.39)	1.04 (0.87, 1.25)	1.13 (0.95, 1.35)
P value	0.114			0.168		
Female in the PLCO						
Dietary intake ^a	2361	<2083.7	2083.7-2280.1	2280.1-2442.7	2442.7-2656.3	>2656.3
Cases/person-years	466/390602	116/77472	95/78008	95/78058	83/78741	77/78322
Multivariable model HR ^b	0.82 (0.66, 1.01)	1.00	0.91 (0.69, 1.21)	0.98 (0.74, 1.31)	0.83 (0.62, 1.11)	0.73 (0.54, 0.98)
P value	0.058			0.03		
Male in the PLCO						
Dietary intake ^a	3108.5	<2731.7	2731.7-2996.2	2996.2-3228.9	3228.9-3551.0	>3551.0
Cases/person-years	626/343406	128/68174	110/68399	133/68534	132/68979	123/69321
Multivariable model HR ^b	1.22 (1.06, 1.40)	1.00	1.02 (0.78, 1.33)	1.31 (1.01, 1.69)	1.32 (1.02, 1.71)	1.23 (0.94, 1.61)
P value	0.004			0.044		
Female in two cohorts						
Dietary intake ^a	2507.6	<2186.2	2186.2-2409.2	2409.2-2610.3	2610.3-2871.3	>2871.3
Cases/person-years	1724/1509925	328/265041	294/278409	355/300244	366/324259	381/341972
Multivariable model HR ^b	1.02 (0.93, 1.13)	1.00	0.95 (0.81, 1.11)	1.10 (0.94, 1.28)	1.06 (0.90, 1.24)	1.04 (0.89, 1.21)
P value	0.651			0.590		

NSCLC, non-small cell lung cancer. ^a, mineral intake was energy-adjusted (mg/day), median intake for continuous and range for quintiles. ^b, Cox proportional hazard models were used to adjust age, body mass index (kg/m²), energy intake (kcal/day), educational level (3 categories), alcohol consumption (g/day), smoking status (never smokers, former smokers <20 pack-years, former smokers ≥20 pack-years, current smokers <20 pack-years, current smokers ≥20 pack-years), history of diabetes (yes or no), and family history of lung cancer (yes or no) for the PLCO trial or family history of cancer (yes or no) for the WHI cohort.

Table S9 Hazard ratios and 95% confidence intervals of SCLC based on categories of dietary mineral intake

	Continuous	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Potassium						
WHI (female only)						
Dietary intake ^a	2620.1	<2154.6	2154.6-2474.5	2474.5-2769.1	2769.1-3140.5	>3140.5
Cases/person-years	104/1107063	25/204969	28/217172	22/225340	13/228607	16/230975
Multivariable model HR ^b	1.01 (0.74, 1.38)	1.00	1.48 (0.85, 2.57)	1.29 (0.72, 2.34)	0.85 (0.43, 1.69)	1.14 (0.60, 2.19)
P value	0.934			0.874		
Female in the PLCO						
Dietary intake ^a	2944.1	<2464.1	2464.1-2797.8	2797.8-3096.9	3096.9-3486.9	>3486.9
Cases/person-years	77/388847	20/77436	15/77545	11/77490	13/78192	18/78183
Multivariable model HR ^b	1.01 (0.74, 1.37)	1.00	0.89 (0.45, 1.76)	0.67 (0.32, 1.44)	0.76 (0.37, 1.56)	0.96 (0.50, 1.84)
P value	0.967			0.839		
Male in the PLCO						
Dietary intake ^a	3489.2	<2936.0	2936.0-3319.1	3319.1-3669.2	3669.2-4141.2	>4141.2
Cases/person-years	109/340959	23/68263	19/67890	23/68001	21/68349	23/68456
Multivariable model HR ^b	1.09 (0.87, 1.37)	1.00	1.04 (0.55, 1.96)	1.26 (0.68, 2.32)	1.09 (0.58, 2.04)	1.11 (0.60, 2.06)
P value	0.474			0.740		
Female in two cohorts						
Dietary intake ^a	2751.2	<2255.2	2255.2-2598.8	2598.8-2908.6	2908.6-3299.1	>3299.1
Cases/person-years	181/1495909	49/310423	37/313390	32/303463	26/293127	37/275507
Multivariable model HR ^b	1.02 (0.82, 1.27)	1.00	1.01 (0.65, 1.56)	0.91 (0.57, 1.44)	0.76 (0.46, 1.25)	1.02 (0.64, 1.61)
P value	0.845			0.916		
Sodium						
WHI (female only)						
Dietary intake ^a	2620.2	<2291.7	2291.7-2522.3	2522.3-2722.4	2722.4-2980.1	>2980.1
Cases/person-years	104/1107063	24/218814	11/220929	23/221658	21/223590	25/222071
Multivariable model HR ^b	1.23 (0.84, 1.80)	1.00	0.57 (0.27, 1.17)	1.31 (0.72, 2.38)	1.22 (0.66, 2.24)	1.37 (0.76, 2.46)
P value	0.289			0.101		
Female in the PLCO						
Dietary intake ^a	2361.8	<2084.4	2084.4-2280.8	2280.8-2443.7	2443.7-2656.9	>2656.9
Cases/person-years	77/388847	27/77185	6/77711	11/77733	17/78303	16/77915
Multivariable model HR ^b	0.90 (0.56, 1.43)	1.00	0.27 (0.11, 0.67)	0.57 (0.27, 1.18)	0.80 (0.43, 1.52)	0.63 (0.33, 1.20)
P value	0.642			0.437		
Male in the PLCO						
Dietary intake ^a	3108.5	<2731.9	2731.9-2996.2	2996.2-3229.2	3229.2-3551.6	>3551.6
Cases/person-years	109/340959	28/67692	16/67906	16/68081	27/68453	22/68828
Multivariable model HR ^b	1.03 (0.75, 1.41)	1.00	0.80 (0.42, 1.52)	0.83 (0.43, 1.59)	1.31 (0.74, 2.33)	0.95 (0.51, 1.75)
P value	0.872			0.729		
Female in two cohorts						
Dietary intake ^a	2507.3	<2186.2	2186.2-2408.9	2408.9-2609.9	2609.9-2871.0	>2871.0
Cases/person-years	181/1495909	47/262551	24/275882	34/297246	36/321279	40/338951
Multivariable model HR ^b	1.07 (0.80, 1.44)	1.00	0.64 (0.38, 1.05)	0.95 (0.60, 1.51)	1.00 (0.63, 1.58)	1.11 (0.70, 1.74)
P value	0.652			0.164		

SCLC, small cell lung cancer. ^a, mineral intake was energy-adjusted (mg/day), median intake for continuous and range for quintiles. ^b, Cox proportional hazard models were used to adjust age, body mass index (kg/m²), energy intake (kcal/day), educational level (3 categories), alcohol consumption (g/day), smoking status (never smokers, former smokers <20 pack-years, former smokers ≥20 pack-years, current smokers <20 pack-years, current smokers ≥20 pack-years), history of diabetes (yes or no), and family history of lung cancer (yes or no) for the PLCO trial or family history of cancer (yes or no) for the WHI cohort.