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Research Article

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Prediagnostic Calcium Intake and Lung Cancer Survival: A Pooled Analysis of 12 Cohort Studies

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Abstract

Background: Lung cancer is the leading cause of cancer death. Little is known about whether prediagnostic nutritional factors may affect survival. We examined the associations of prediagnostic calcium intake from foods and/or supplements with lung cancer survival.

Methods: The present analysis included 23,882 incident, primary lung cancer patients from 12 prospective cohort studies. Dietary calcium intake was assessed using food-frequency questionnaires at baseline in each cohort and standardized to caloric intake of 2,000 kcal/d for women and 2,500 kcal/d for men. Stratified, multivariable-adjusted Cox regression was applied to compute hazard ratios (HR) and 95% confidence intervals (CI).

Results: The 5-year survival rates were 56%, 21%, and 5.7% for localized, regional, and distant stage lung cancer, respectively. Low prediagnostic dietary calcium intake (<500–600 mg/d, less than half of the recommendation) was associated with a small increase in risk of death compared with recommended calcium intakes (800–1,200 mg/d); HR (95% CI) was 1.07 (1.01–1.13) after adjusting for age, stage, histology, grade, smoking status, pack-years, and other potential prognostic factors. The association between low calcium intake and higher lung cancer mortality was evident primarily among localized/regional stage patients, with HR (95% CI) of 1.15 (1.04–1.27). No association was found for supplemental calcium with survival in the multivariable-adjusted model.

Conclusions: This large pooled analysis is the first, to our knowledge, to indicate that low prediagnostic dietary calcium intake may be associated with poorer survival among early-stage lung cancer patients.

Impact: This multinational prospective study linked low calcium intake to lung cancer prognosis. *Cancer Epidemiol Biomarkers Prev; 1–11. ©2017 AACR.*

Lung cancer is the leading cause of cancer death worldwide, accounting for 1.6 million deaths (20% of all cancer deaths) annually (1). Most lung cancer patients are diagnosed at advanced stages; the 5-year survival rate is only ∼18% in the United States and is even lower in other countries (2–4). While its prognosis largely depends on stage, histologic type, treatment options, and

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patient demographics and comorbidity status (2, 5, 6), emerging evidence suggests that prediagnostic nutrition and lifestyle factors may also influence lung cancer survival (7–9).

Both experimental and epidemiological studies have suggested potential roles of calcium in cancer development and progression (10). Besides its well-known effects on bone health, calcium intake and calcium homeostasis can affect cell proliferation, differentiation, and apoptosis, parathyroid hormone (PTH) and PTH-related peptide, vitamin D metabolism and signaling, angiogenesis, and immune response (11, 12). Compromised bone health and impaired calcium homeostasis due to a long-term calcium insufficiency may promote tumor progression and metastasis. Cohort studies and meta-analyses have linked adequate calcium intake with decreased overall cancer risk and risks of colorectal, breast, and prostate cancers (13–19). Evidence, although limited, has also linked calcium intake with lung cancer risk (20–22). However, few cohort studies have examined the association of prediagnostic calcium intake with cancer survival, and none explicitly with lung cancer survival (23, 24).

We investigated prediagnostic calcium intake from foods and supplements in relation to lung cancer survival using data from a large pooling project, the Calcium and Lung Cancer Pooling Project. Individual-level data of ∼1.7 million participants from 12 prospective cohort studies in the United States, Europe, and Asia were pooled, resulting in 23,882 incident, primary lung cancer cases. We examined the association among all cases combined and separately by major lung cancer prognostic factors, including age, stage, and histology. We focused our analyses more on the survival of localized and regional stage patients because it is unlikely that the prognosis of distant stage lung cancer would be significantly influenced by prediagnostic nutritional factors, given its high fatality rate and short survival time.

Materials and Methods

Study populations

Participating studies included eight US cohorts: the National Institutes of Health–AARP study (NIH-AARP; ref. 25), Health Professionals' Follow-Up Study (HPFS; ref. 26), Nurses' Health Study I (NHS; ref. 27), Iowa Women's Health Study (IWHS; ref. 28), Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO; ref. 29), Southern Community Cohort Study (SCCS; ref. 30), Vitamins and Lifestyle Cohort Study (VITAL; ref. 31), and Women's Health Initiative Observational Study (WHI; ref. 32); one European cohort: the European Prospective Investigation into Cancer and Nutrition Cohort (EPIC; ref. 33); and three Asian cohorts: the Japan Public Health Center-based Prospective Study cohort I and II (JPHC; ref. 34), Shanghai Men's Health Study (SMHS; ref. 35), and Shanghai Women's Health Study (SWHS; ref. 36). Each study was approved by the Institutional Review Board at local institutions; the pooling project was approved by the Vanderbilt University Institutional Review Board.

Assessment of dietary and supplemental calcium intake

Usual dietary intakes were assessed at baseline in each cohort using a self- or interviewer-administered food-frequency questionnaire (FFQ) as described in previous publications (37–48). The FFQs usually inquired about habitual consumption of common food items over the past 12 months and were validated against 24-hour dietary recalls, 7-day food records, or dietary biomarkers. Daily food intakes were estimated based on the frequency and amount of consumption and were linked to country/region-specific food composition tables to calculate intakes of energy (kcal/d), calcium (mg/d), and other nutrients. In the current study, dietary intakes were adjusted for total energy intake using the nutrient density method (49) and standardized to intakes per 2,000 kcal for women and per 2,500 kcal for men. Intake of supplemental calcium was assessed in eight US cohorts. Participants were asked whether in the past year they generally took supplements (multivitamins and/or single calcium supplements); and if yes, how often (from less than once per week to every day) and how much they usually took (from <200 mg/d to >1,000 mg/d for calcium). Most cohorts estimated supplemental calcium intakes from both calcium supplements and multivitamins, except that the SCCS asked only about the use of calcium supplements.

Assessment of lung cancer incidence and survival

Our primary outcome is overall survival time, calculated by counting from the date of lung cancer diagnosis to the date of death or end of follow-up, whichever came first. Incident cancer cases and the vital status of cancer patients were identified in each cohort through linkages with national/regional cancer registries and death registries, follow-up interviews, review of medical records and/or death certificates, or these methods combined. Cancers of the bronchus and lung were ascertained by the *International Classification of Diseases* (ICD) codes: 162 (ICD-9) or C34 (ICD-10). Year of diagnosis and whether lung cancer was the underlying cause of death was acquired from the cohorts. Clinical information was obtained when available, including stage, histologic type, and grade. We harmonized tumor information across studies as follows: stage—localized, regional, distant, and unknown; histologic type—adenocarcinoma, squamous cell carcinoma, other non–small cell lung cancer, small cell lung cancer, and other; and grade—well-, moderately, and poorly differentiated, undifferentiated, and unknown.

Assessment of non-dietary covariates

Baseline information on sociodemographics, lifestyles, medical history, and anthropometrics was obtained from each cohort and harmonized for the current study, including age at baseline and at diagnosis (years, integer), sex (male or female), race/ethnicity (non-Hispanic white, Black, Asian, or other), educational attainment (≤high school, vocational school or some college, college or graduate school), smoking status (never, former, or current use of cigarettes, cigars, or pipe), pack-years of cigarette smoking (continuous), alcohol drinking status [none, moderate, or heavy (>14 g/d for women and >28 g/d for men)], physical activity level [low, middle, or high (cutoffs: zero leisure-time physical activity and median of non-zero leisure-time physical activity assessed by metabolic equivalents or hours, or tertile of total physical activity metabolic equivalents)], history of diabetes (yes or no), obesity status (body mass index [BMI] <18.5, 18.5–24.99, 25.0–29.99, or ≥30 kg/m^2), and in women, postmenopausal status (yes or no) and use of hormone therapy (never or ever).

The proportion of missing values was generally <10% in each cohort for these covariates. If the proportion of missing values was <3%, we assigned the median nonmissing value for continuous variables (e.g., BMI) and the most frequent category for categorical variables (e.g., education). If the proportion of missing variables was ≥3%, we used a multivariate imputation to estimate missing

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value based on other covariates, calcium intake, energy intake, and lung cancer and death outcomes (SAS PROC MI procedure). Missing data imputation was processed for each cohort separately. Of note, in the JPHC, Cohort I did not have data on physical activity metabolic equivalents and Cohort II did not collect information on education level; we imputed these two variables using the above described method in JPHC Cohort I and II data combined.

Analytic population

We excluded participants from the current study if they had (i) a history of any cancer except non-melanoma skin cancer prior to lung cancer, (ii) missing diagnosis or survival time information, (iii) missing calcium intakes or smoking status information, or (iv) implausible total energy intake (beyond three standard deviations of the cohort- and sex-specific log-transformed mean energy intake or beyond the cohort predetermined range). A total of 24,440 incident primary lung cancer cases among 1,679,842 participants of the pooling project were considered eligible. We further excluded 11 cases with cancer *in situ* and 547 cases with data missing on both stage and histology, leaving 23,882 incident lung cancer cases in our analyses.

Statistical analysis

Usual dietary calcium intakes were compared among lung cancer patients with different baseline characteristics and tumor features using a general linear model (adjusted for age at baseline, sex, and total energy intake). Corresponding 5-year survival rates were estimated by the life-table method and *P* for differences was evaluated via the log-rank test with Bonferroni correction. The Cox proportional hazard model was used to estimate hazard ratios (HR) and 95% confidence intervals (CI), stratified by cohort, year of lung cancer diagnosis (5-year intervals from earlier than 1990 to later than 2010), and time interval between dietary assessment and lung cancer diagnosis (<4, 4–7, >7–10, and >10 years, according to the quartile distribution). Potential confounders associated with calcium intake and/or lung cancer survival were adjusted for, including age at diagnosis, sex, race/ethnicity, education, smoking status, pack-years of cigarette smoking, total energy intake, alcohol consumption, physical activity, history of diabetes, obesity status, use of hormone therapy in women, and the stage, histologic type, and grade of lung cancer. Considering the interplay of calcium, magnesium, vitamin D, and phosphorus, we further adjusted for, when data were available, dietary intakes of magnesium (in all cohorts), vitamin D (in 9 cohorts), and phosphorus (in all cohorts), individually or together, with or without interaction terms with calcium. However, the associations of dietary calcium with lung cancer survival were basically unchanged, so these nutrients were not included in the final model.

Calcium intakes were analyzed as categorical variables and as continuous variables. We used the *Dietary Reference Intakes* recommended by the US Institute of Medicine as project-wide cutoff points for dietary and total calcium intakes (11). Briefly, for men ages 19 to 70 years and women ages 19 to 50 years, the estimated average requirement (EAR) of calcium is 800 mg/d and the recommended dietary allowance (RDA) is 1,000 mg/d; for men >70 years and women >50 years, the EAR is 1,000 mg/d and the RDA is 1,200 mg/d. Participants were classified into five groups based on their calcium intakes: <0.5 RDA, 0.5 RDA to EAR, EAR to RDA, RDA to 1.5 RDA, or >1.5 RDA. The cutoff points for supplemental calcium intake were 0, 200, 500, and 1,000 mg/d. A joint analysis was conducted by dietary and supplemental calcium intakes to examine specifically the association for supplemental calcium among those with low dietary calcium intake and the association for dietary calcium among those with no or little supplemental calcium intake. Calcium intakes were modeled continuously in restricted cubic spline regression to examine dose–response associations. Patients in the sex-specific top and bottom 1% of calcium intakes were excluded. Three knots were chosen based on model fitness, at the 5th, 50th, and 95th percentiles (corresponding to 425, 910, and 1625 mg/d). The referent intake was 900 mg/d, and all potential confounders were included in the spline regression.

Stratified analyses were performed by potential effect modifiers, including age at diagnosis, sex, race/ethnicity, education, smoking, other lifestyle factors, stage, histologic type, grade, and time interval between dietary assessment and cancer diagnosis. *P* for interaction was evaluated via likelihood ratio test comparing models with and without the interaction term (calcium intake category × stratification variable). Sensitivity analyses were conducted by excluding those diagnosed with lung cancer within two years after baseline, by excluding those who died or were lost to follow-up within 3 months after diagnoses, or by examining lung cancer-specific mortality. Meta-analysis was applied as an alternative approach to pooled analysis. Cohort-specific HRs and 95% CI were calculated and then combined using a fixed-effect model because no significant between-study heterogeneity was detected. Two-sided $P < 0.05$ were considered statistically significant. All analyses were conducted using SAS, version 9.4 (SAS Institute, Inc.).

Results

Among 1,679,842 men and women from 12 cohort studies, 23,882 incident primary lung cancer cases were identified during a median follow-up of 7 years (interquartile range, 4–10 years); 19,538 died (16,279 from lung cancer) with a median survival time of 11 months (interquartile range, 4–34 months). The overall 5-year survival rate was 21.3%. Higher survival rates were associated with younger age at diagnosis, female gender, never smoking, fewer pack-years if ever smoked, no history of diabetes, and higher level of physical activity (Table 1). Particularly low 5-year survival rates were found for small cell lung cancer (9.7%), distant stage cancer (5.7%), and undifferentiated tumor cells (10.4%). Dietary calcium intakes were higher in the US and European cohorts than in Asian cohorts (Supplementary Table S1) and were positively associated with past smoking, physical activity, moderate alcohol consumption, BMI, history of diabetes, and use of hormone therapy in women. Prediagnostic dietary calcium intakes did not vary by tumor characteristics.

A majority of lung cancer patients (78.1%) reported usual dietary calcium intakes from half to 1.5-fold of the RDA; 15.5% of patients consumed <0.5 RDA and 6.4% consumed >1.5 RDA. Low dietary calcium intake (<0.5 RDA) was associated with a small but significantly increased risk of death compared with the recommended calcium intake (800–1,200 mg/d; Table 2); the HRs (95% CIs) were 1.08 (1.03–1.14) in the model adjusted for age, sex, smoking status, pack-years, and total energy intake; and 1.07 (1.01–1.13) when further adjusted for known prognostic factors, including stage, histology, and grade. Supplemental calcium intake was not associated with lung cancer survival, although in the basic adjustment model, 200–500 mg/d

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supplemental calcium appeared to be associated with slightly reduced mortality (Table 2).

In stratified analysis, the association of low prediagnostic calcium intake with poor lung cancer survival was more evident in men than in women ($P_{interaction} = 0.01$), and in early-stage than in distant-stage cases ($P_{interaction} = 0.006$; Fig. 1). In particular, low calcium intake (<0.5 RDA vs. RDA) was associated with significantly increased mortality in male patients [HR (95% CI), 1.15

Table 1. Characteristics, dietary calcium intake, and 5-year survival rate of lung cancer cases ($n = 23,882$)

Characteristics	Cases, *n*	Deaths, *n*	Dietary calcium intake, mg/d[a]	*P* for calcium intake[b]	5-Year survival rate (95% CI), %	*P* for survival rate[b]
Age at diagnosis						
<65 years	6,439	5,087	883 ± 413	ref	23.8 (22.8–24.9)	ref
65–75 years	13,263	11,039	930 ± 412	<0.0001	21.0 (20.3–21.7)	<0.0001
>75 years	4,180	3,412	947 ± 412	<0.0001	18.0 (16.8–19.2)	<0.0001
Sex						
Female	11,574	9,021	897 ± 425	ref	25.3 (24.5–26.2)	ref
Male	12,308	10,517	944 ± 424	<0.0001	17.5 (16.8–18.2)	<0.0001
Race						
White	19,448	16,137	979 ± 389	ref	21.1 (20.6–21.7)	ref
Black	1,037	780	789 ± 392	<0.0001	22.5 (19.9–25.2)	0.99
Asian	3,140	2,408	593 ± 396	<0.0001	21.8 (20.3–23.3)	0.76
Other	257	213	924 ± 388	0.14	20.0 (15.3–25.2)	0.99
Education						
High school	9,947	8,181	889 ± 409	ref	18.8 (18.0–19.6)	ref
Vocational school/Some college	8,140	6,668	963 ± 410	<0.0001	22.2 (21.2–23.1)	<0.0001
College and graduate school	5,795	4,689	912 ± 414	0.002	23.6 (22.5–24.6)	<0.0001
Tobacco smoking						
Never	2,948	2,063	867 ± 415	ref	31.6 (29.8–33.3)	ref
Former	9,589	7,972	975 ± 420	<0.0001	21.4 (20.6–22.2)	<0.0001
Current	11,345	9,503	889 ± 415	0.04	18.6 (17.8–19.3)	<0.0001
Smoking pack-years in cigarette smokers						
<30 pack-years	6,187	4,876	946 ± 412	ref	22.8 (21.7–23.9)	ref
30–50 pack-years	7,442	6,275	917 ± 410	<0.0001	19.4 (18.5–20.3)	<0.0001
>50 pack-years	7,134	6,173	923 ± 418	0.005	18.0 (17.1–18.9)	<0.0001
History of diabetes						
No	22,028	17,918	913 ± 409	ref	21.8 (21.2–22.3)	ref
Yes	1,854	1,620	1007 ± 411	<0.0001	15.5 (13.9–17.2)	<0.0001
Physical activity						
Low	5,674	4,565	836 ± 407	ref	20.0 (18.9–21.0)	ref
Middle	9,157	7,631	924 ± 407	<0.0001	20.7 (19.9–21.6)	0.22
High	9,051	7,342	969 ± 406	<0.0001	22.6 (21.7–23.5)	<0.0001
Body mass index						
<18.5 kg/m^2	525	423	796 ± 408	0.0002	21.7 (20.9–22.5)	0.35
18.5–24.99 kg/m^2	10,758	8,768	889 ± 410	ref	20.3 (16.9–24.0)	ref
25.0–29.99 kg/m^2	8,888	7,294	948 ± 411	<0.0001	21.0 (20.1–21.9)	0.86
≥30.0 kg/m^2	3,711	3,053	963 ± 408	<0.0001	20.8 (19.5–22.2)	0.68
Alcohol consumption						
None	7,265	5,849	909 ± 404	ref	21.4 (20.5–22.4)	ref
Moderate	11,414	9,341	989 ± 404	<0.0001	21.9 (21.2–22.7)	0.98
Heavy	5,203	4,348	786 ± 411	<0.0001	19.5 (18.5–20.6)	0.02
Hormone therapy among women						
No	6,686	5,263	867 ± 388	ref	24.1 (23.1–25.2)	ref
Yes	4,888	3,758	931 ± 388	<0.0001	27.0 (25.7–28.3)	<0.0001
Histological type						
Adenocarcinoma	9,621	7,324	922 ± 411	ref	27.7 (26.8–28.7)	ref
Squamous cell carcinoma	4,318	3,468	913 ± 411	0.99	24.7 (23.4–26.0)	<0.0001
Other non–small cell carcinoma	3,414	2,769	958 ± 409	0.001	21.6 (20.2–23.0)	<0.0001
Small cell carcinoma	3,210	2,955	945 ± 409	0.05	9.7 (8.7–10.8)	<0.0001
All other	3,319	3,022	861 ± 410	<0.0001	9.6 (8.7–10.7)	<0.0001
Tumor stage						
Localized	3,489	1,823	921 ± 410	ref	56.4 (54.6–58.1)	ref
Regional	4,524	3,713	905 ± 410	0.54	21.1 (20.0–22.3)	<0.0001
Distant	6,752	6,327	904 ± 412	0.31	5.7 (5.2–6.3)	<0.0001
Unknown	9,117	7,675	940 ± 416	0.12	20.4 (19.5–21.2)	<0.0001
Tumor grade						
Well differentiated	1,213	592	843 ± 409	ref	57.9 (54.9–60.8)	ref
Moderately differentiated	2,791	1,953	921 ± 409	<0.0001	37.3 (35.5–39.1)	0.66
Poorly differentiated	4,560	3,742	925 ± 411	<0.0001	22.2 (21.0–23.4)	<0.0001
Undifferentiated	1,838	1,714	831 ± 409	0.99	10.4 (9.0–11.8)	<0.0001
Unknown	13,480	11,537	938 ± 410	<0.0001	16.2 (15.5–16.8)	<0.0001

[a]Mean ± SD, adjusted for age, sex, and total energy intake, per 2,000 kcal for women and per 2,500 kcal for men.
[b]*P* values were corrected for multiple comparisons using the Bonferroni method.

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Table 2. Pooled analyses of calcium intake and lung cancer survival ($n = 23,882$)

Calcium intakes	Deaths/cases, *n*	Hazard ratio (95% CI)	
		Model 1[a]	Model 2[b]
Dietary calcium intake, mg/d[c]			
<500 or <600	3,047/3,705	1.08 (1.03–1.14)	1.07 (1.01–1.13)
500–800 or 600–1,000	7,463/9,190	1.04 (1.00–1.08)	1.04 (1.00–1.09)
800–1,000 or 1,000–1,200	3,531/4,362	1.00 (ref)	1.00 (ref)
1,000–1,500 or 1,200–1,800	4,205/5,092	1.02 (0.97–1.07)	1.05 (1.01–1.10)
>1,500 or >1,800	1,292/1,533	1.03 (0.96–1.09)	1.04 (0.97–1.11)
Dietary and supplemental calcium intake, mg/d[c,d]			
<500 or <600	1,119/1,352	1.04 (0.96–1.11)	1.02 (0.95–1.10)
500–800 or 600–1000	4,333/5,212	1.01 (0.96–1.06)	0.99 (0.94–1.04)
800–1,000 or 1,000–1,200	2,695/3,216	1.00 (ref)	1.00 (ref)
1,000–1,500 or 1,200–1,800	4,364/5,290	0.97 (0.93–1.02)	1.01 (0.96–1.06)
>1,500 or >1,800	2,507/3,067	0.97 (0.91–1.02)	0.99 (0.94–1.05)
Supplemental calcium intake, mg/d[d]			
None	7,850/9,387	1.00 (ref)	1.00 (ref)
0–200	3,524/4,158	0.99 (0.95–1.04)	1.01 (0.97–1.06)
200–500	1,557/1,969	0.95 (0.90–1.00)	1.00 (0.94–1.05)
500–1,000	1,391/1,743	0.96 (0.91–1.02)	1.00 (0.94–1.06)
>1,000	696/880	0.97 (0.89–1.05)	1.01 (0.93–1.10)

[a]Cox model was stratified by cohort, year of lung cancer diagnosis, and time interval between dietary assessment and lung cancer diagnosis and adjusted for age at diagnosis, sex, smoking status, smoking pack-years, and total energy intake.

[b]Additionally adjusted for race, education, alcohol consumption, history of diabetes, physical activity level, obesity status, hormone therapy in women, and the histological type, stage, and grade of lung cancer.

[c]For men ≤70 years and women ≤50 years, the recommended dietary allowance (RDA) of calcium is 1,000 mg/d and the estimated average requirement (EAR) is 800 mg/d. For men >70 years and women >50 years, RDA is 1,200 mg/d and EAR is 1,000 mg/d. Calcium intakes were categorized into five groups: <0.5 RDA, 0.5 RDA to EAR, EAR to RDA, RDA to 1.5 RDA, and >1.5 RDA.

[d]Supplemental calcium intake data were available only in eight US cohorts, $n = 18,137$.

(1.06–1.25)], and in localized/regional stage patients [HR (95% CI), 1.15 (1.04–1.27)]. We did not observe significant interactions by other potential effect modifiers (Fig. 1). Kaplan–Meier survival curves by dietary calcium intakes, stratified by stage, histologic type, and grade, are shown in Supplementary Fig. S1.

We thereafter focused our analyses among early-stage cases (Table 3, $n = 8,013$). Low dietary calcium intake (<0.5 RDA vs. RDA) was significantly associated with increased lung cancer mortality in early-stage patients, especially for men [HR (95% CI), 1.25 (1.08, 1.45)] and never smokers [HR (95% CI), 1.45 (1.01–2.08)]. Notably, we also observed that a very high calcium intake (>1.5 RDA vs. RDA) was associated with increased mortality in early-stage female patients [HR (95% CI), 1.33 (1.05–1.70)], although there were only 89 deaths and 134 female patients with a calcium intake this high. Among early-stage patients with low dietary calcium intake, supplemental calcium intake showed a possible trend of inverse association with mortality; compared with no or little supplemental calcium (<200 mg/d), HRs (95% CIs) were 0.90 (0.71–1.13) and 0.68 (0.44–1.07) for supplemental calcium of 200 to 1,000 and >1,000 mg/d, respectively. Meanwhile, among patients with no or little supplemental calcium intake, the HR (95% CI) for a low dietary calcium intake (<0.5 RDA vs. RDA) was 1.17 (1.02–1.35).

In cubic spline modeling, the lowest mortality among early-stage lung cancer patients was observed for dietary calcium intakes of 800 to 1200 mg/d (Fig. 2A, $P = 0.03$). Consistent with the above findings, low dietary calcium intake was associated with increased mortality, especially among early-stage male patients (Fig. 2B). Meanwhile, very high calcium intake may also be associated with increased mortality among early-stage female patients (Fig. 2C), although the confidence interval was very wide.

Results were robust in sensitivity analyses and in meta-analysis. The HRs (95% CI) in early-stage cases for low dietary calcium intake were 1.14 (1.02–1.28) after excluding those diagnosed within two years after baseline ($n = 6,362$), 1.17 (1.05–1.30) after excluding those who died within three months after diagnosis ($n = 7,246$), 1.15 (1.02–1.28) for lung cancer–specific deaths (cases = 4,246), and 1.14 (1.02–1.28) in a fixed-effect meta-analysis ($P_{heterogeneity} = 0.39$; Supplementary Fig. S2).

Discussion

In this large pooled analysis of 12 cohort studies, we observed that low prediagnostic dietary calcium intake (<500–600 mg/d) was associated with a slightly increased risk of death among lung cancer patients, after taking other prognostic factors into account. The lowest mortality was observed for dietary calcium intakes of 800 to 1,200 mg/d; further increase in calcium intake did not confer additional benefit. The association between low prediagnostic calcium intake and lung cancer survival was primarily confined to early-stage patients. No significant association was found for prediagnostic supplemental calcium intake with lung cancer survival.

Our study provides the first epidemiological evidence that long-term insufficient calcium intake may influence lung cancer prognosis, especially for early-stage patients, when cancer has not spread to other organs. Metastasis is the major reason for cancer-related deaths (50). For lung cancer, a frequent site of metastasis is the bone, occurring in nearly 40% of patients (51–53). Impaired bone metabolism and calcium homeostasis due to a long-term calcium insufficiency may facilitate bone metastasis and promote tumor growth in lung cancer. Calcium is an essential nutrient for bone remodeling (formation and resorption). A prolonged calcium deficiency leads to increased bone resorption and compromised bone health (11). When the circulating calcium level drops because of a low supply, multiple signaling pathways, hormones, and cytokines are affected. Directly, calcium is a second messenger and calcium signaling regulates cell differentiation, proliferation,

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and apoptosis (10, 54). Indirectly, to maintain a proper extracellular calcium level, the body upregulates secretions of PTH, 1,25-dihydroxyvitamin D, as well as several bone- or T cell–derived cytokines and growth factors, e.g., receptor activator of nuclear factor kappa-B ligand (RANKL), macrophage colony-stimulating factor, vascular endothelial growth factor, and interleukin-6 (55). Activation of these pathways enhances tumor growth, promotes angiogenesis, and accelerates metastasis (52, 55). During tumor progression, bone remodeling and calcium homeostasis are further disturbed. Tumor cells secrete factors that increase RANKL expression and bone resorption; in turn, growth factors released from the bone stimulate tumor growth and metastasis. This vicious cycle of bone destruction and tumor progression is well documented as an unfavorable prognostic factor of lung cancer (53, 56, 57). A few clinic-based studies have suggested that low blood calcium level and high bone resorption markers are associated with increased bone metastasis and decreased survival time among newly diagnosed lung cancer patients, after controlling for other clinicopathological factors (58–60). Therefore, bone-targeted therapies have been used to reduce bone metastases and prolong lung cancer survival (61, 62), and assessments of bone condition and bone metastasis have been recommended throughout lung cancer treatment (63, 64). Although limited by a lack of clinical information on patients' metastasis status or their blood calcium concentration or bone imaging data, our study is the first epidemiologic study to show that patients with habitually low calcium intakes were at a high risk of death. Our findings suggest that assessments of bone health and calcium homeostasis may benefit these patients, especially those diagnosed at early stages, by allowing for a proper intervention.

A U-shaped relationship was found in recent meta-analyses of calcium intake with mortality from all causes, cardiovascular disease, and cancer (65, 66). Our results also suggest a possible U-shaped association between dietary calcium and lung cancer survival with an optimal intake around 1,000 mg/d; intakes of <500 mg/d (especially among early-stage men) or >1,800 mg/d (especially among early-stage women) were both associated with increased mortality. However, the number of patients with

Subgroups	Cases (deaths), *n*	Prediagnostic dietary calcium intake, mg/d	5-year survival rate, %	*P* for interaction
Age at diagnosis				0.53
<65 years	6,439 (5,087)	883 ± 413	23.8	
65–75 years	13,263 (11,039)	930 ± 412	21.0	
>75 years	4,180 (3,412)	947 ± 412	18.0	
Sex				**0.01**
Female	11,574 (9,021)	897 ± 425	25.3	
Male	12,308 (10,517)	944 ± 424	17.5	
Race/Ethnicity				0.28
White	19,448 (16,137)	979 ± 389	21.1	
Black	1,037 (780)	789 ± 392	22.5	
Asian	3,140 (2,408)	593 ± 396	21.8	
Tobacco smoking status				0.51
Never	2,948 (2,063)	867 ± 415	31.6	
Former	9,589 (7,972)	975 ± 420	21.4	
Current	11,345 (9,503)	889 ± 415	18.6	
Tumor stage				**0.006**
Localized & regional stage	8,013 (5,536)	912 ± 411	36.0	
Distant stage	6,752 (6,327)	904 ± 412	5.7	
Histologic type				0.42
Adenocarcinoma	9,621 (7,324)	922 ± 411	27.7	
Squamous cell carcinoma	4,318 (3,468)	913 ± 411	24.7	
Other non–small cell carcinoma	3,414 (2,769)	958 ± 409	21.6	
Small-cell carcinoma	3,210 (2,955)	945 ± 409	9.7	
Histologic grade				0.11
Well & moderately differentiated	4,004 (2,545)	898 ± 410	43.3	
Poorly & undifferentiated	6,398 (5,456)	900 ± 411	18.7	
Time interval from baseline survey to cancer diagnosis				0.64
<7 years	11,432 (9,912)	928 ± 418	19.9	
≥7 years	12,450 (9,626)	914 ± 417	22.6	

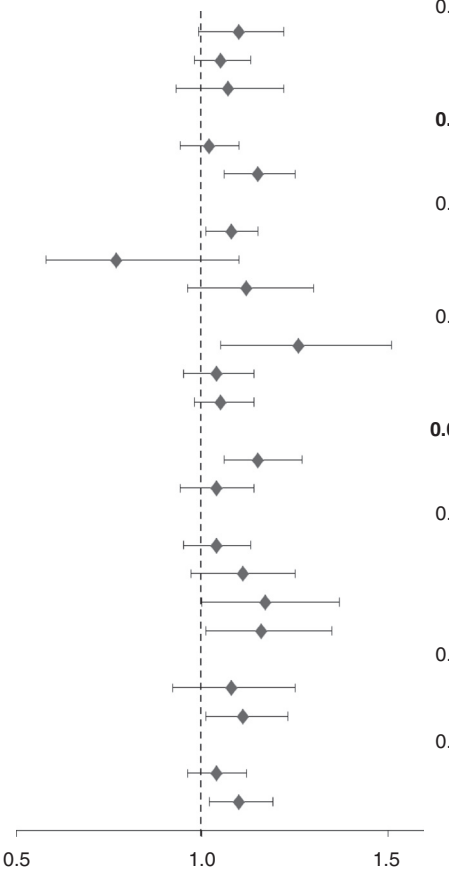

Figure 1.

Risk of death by prediagnostic dietary calcium intake (low vs. recommended intake) in subgroups of the Calcium and Lung Cancer Pooling Project. Low intake was defined as calcium intake less than half of the recommended dietary allowance (RDA), which is less than 500 mg/d for men ≤70 years and women ≤50 years, or less than 600 mg/d for men >70 years and women >50 years. Recommended intake was defined as calcium intake between the estimated average requirement (EAR) and RDA, which is 800 to 1,000 mg/d for men ≤70 years and women ≤50 years, or 1,000 to 1,200 mg/d for men >70 years and women >50 years. The same stratified, multivariable-adjusted Cox model (Model 2) was used as shown in Table 2 footnote.

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Table 3. Dietary calcium intake and lung cancer survival in early-stage cases (n = 8,013)[a]

Dietary calcium intake, mg/d	Deaths/cases, n	Hazard ratio (95% CI)	
		Model 1	Model 2
All early-stage lung cancer cases			
<500 or <600	928/1,342	1.12 (1.01–1.24)	1.15 (1.04–1.27)
500–800 or 600–1,000	2,083/3,065	1.06 (0.98–1.14)	1.06 (0.98–1.14)
800–1,000 or 1,000–1,200	990/1,442	1.00 (ref)	1.00 (ref)
1,000–1500 or 1,200–1,800	1,164/1,660	1.00 (0.92–1.09)	1.04 (0.96–1.14)
>1,500 or >1,800	371/504	0.99 (0.88–1.12)	1.07 (0.95–1.21)
Female			
<500 or <600	542/837	1.10 (0.95–1.28)	1.08 (0.92–1.25)
500–800 or 600–1,000	1,076/1,727	1.09 (0.96–1.24)	1.03 (0.90–1.17)
800–1,000 or 1,000–1,200	311/547	1.00 (ref)	1.00 (ref)
1,000–1,500 or 1,200–1,800	368/591	1.11 (0.95–1.30)	1.12 (0.96–1.31)
>1,500 or >1,800	89/134	1.25 (0.98–1.58)	1.33 (1.05–1.70)
Male			
<500 or <600	386/505	1.17 (1.01–1.36)	1.25 (1.08–1.45)
500–800 or 600–1,000	1,007/1,338	1.04 (0.94–1.15)	1.07 (0.97–1.18)
800–1,000 or 1,000–1,200	679/895	1.00 (ref)	1.00 (ref)
1,000–1,500 or 1,200–1,800	796/1,069	0.94 (0.85–1.05)	0.99 (0.90–1.10)
>1,500 or >1,800	282/370	0.93 (0.80–1.06)	0.99 (0.86–1.14)
Whites			
<500 or <600	507/691	1.12 (1.00–1.26)	1.16 (1.03–1.31)
500–800 or 600–1,000	1,673/2,377	1.05 (0.97–1.15)	1.06 (0.97–1.15)
800–1,000 or 1,000–1,200	873/1,254	1.00 (ref)	1.00 (ref)
1,000–1,500 or 1,200–1,800	1,103/1,539	1.02 (0.93–1.11)	1.05 (0.96–1.15)
>1,500 or >1,800	358/480	1.01 (0.89–1.15)	1.09 (0.96–1.23)
Asians			
<500 or <600	363/548	1.15 (0.97–1.35)	1.20 (1.01–1.43)
500–1,000 or 600–1,200	326/562	1.00 (ref)	1.00 (ref)
>1,000 or >1,200	33/76	0.73 (0.50–1.05)	0.76 (0.52–1.12)
Blacks			
<500 or <600	53/93	0.78 (0.55–1.09)	0.79 (0.55–1.14)
500–1,000 or 600–1,200	171/269	1.00 (ref)	1.00 (ref)
>1,000 or >1,200	25/47	0.60 (0.38–0.95)	0.77 (0.46–1.27)
Never smokers			
<500 or <600	143/260	1.32 (0.94–1.85)	1.45 (1.01–2.08)
500–800 or 600–1,000	204/410	1.06 (0.73–1.41)	1.12 (0.82–1.53)
800–1,000 or 1,000–1,200	71/146	1.00 (ref)	1.00 (ref)
1,000–1500 or 1,200–1,800	100/181	1.01 (0.73–1.40)	1.06 (0.76–1.49)
>1,500 or >1,800	20/41	0.84 (0.50–1.42)	0.86 (0.50–1.47)
Former/current smokers			
<500 or <600	785/1,082	1.09 (0.98–1.21)	1.12 (1.01–1.25)
500–800 or 600–1,000	1,879/2,655	1.06 (0.91–1.09)	1.05 (0.97–1.14)
800–1,000 or 1,000–1,200	919/1,296	1.00 (ref)	1.00 (ref)
1,000–1,500 or 1,200–1,800	1,064/1,479	1.00 (0.91–1.09)	1.04 (0.95–1.14)
>1,500 or >1,800	351/463	1.01 (0.89–1.15)	1.09 (0.96–1.23)
Localized stage cases			
<500 or <600	293/579	1.14 (0.96–1.37)	1.16 (0.97–1.40)
500–800 or 600–1,000	696/1,346	1.12 (0.97–1.29)	1.12 (0.97–1.29)
800–1,000 or 1,000–1,200	304/604	1.00 (ref)	1.00 (ref)
1,000–1,500 or 1,200–1,800	405/739	1.05 (0.91–1.23)	1.10 (0.95–1.28)
>1,500 or >1,800	125/221	0.93 (0.75–1.15)	0.97 (0.78–1.20)
Regional stage cases			
<500 or <600	635/763	1.07 (0.95–1.21)	1.10 (0.97–1.25)
500–800 or 600–1,000	1,387/1,719	1.01 (0.91–1.11)	1.02 (0.93–1.12)
800–1,000 or 1,000–1,200	686/838	1.00 (ref)	1.00 (ref)
1,000–1,500 or 1,200–1,800	759/921	1.00 (0.90–1.11)	1.01 (0.90–1.12)
>1,500 or >1,800	246/283	1.10 (0.95–1.27)	1.11 (0.96–1.29)

[a]The same covariates and calcium cutoffs as shown in the footnote of Table 2. P for interaction was 0.02 for calcium intake levels with sex, 0.68 with race/ethnicity, 0.70 with smoking, and 0.47 with stage.

excessive dietary calcium intake was too small to draw conclusions from this observation. In addition, the increased risk among very high calcium consumers may indirectly reflect a history of calcium deficiency and poor bone health, leading to a subsequent increase in calcium consumption, particularly for women who are more likely to be affected by and diagnosed with osteoporosis. Although the sex-differential associations we observed could be due to chance, they warrant further investigation. Possible explanations include gender differences in calcium intake level, lung cancer histology, estrogen exposure, and lifestyle habits.

Our study did not find a significant association between supplemental calcium intake and lung cancer survival among the 18,137 incident cases from eight US cohorts that collected this information. The null association may be due to the fact that fewer

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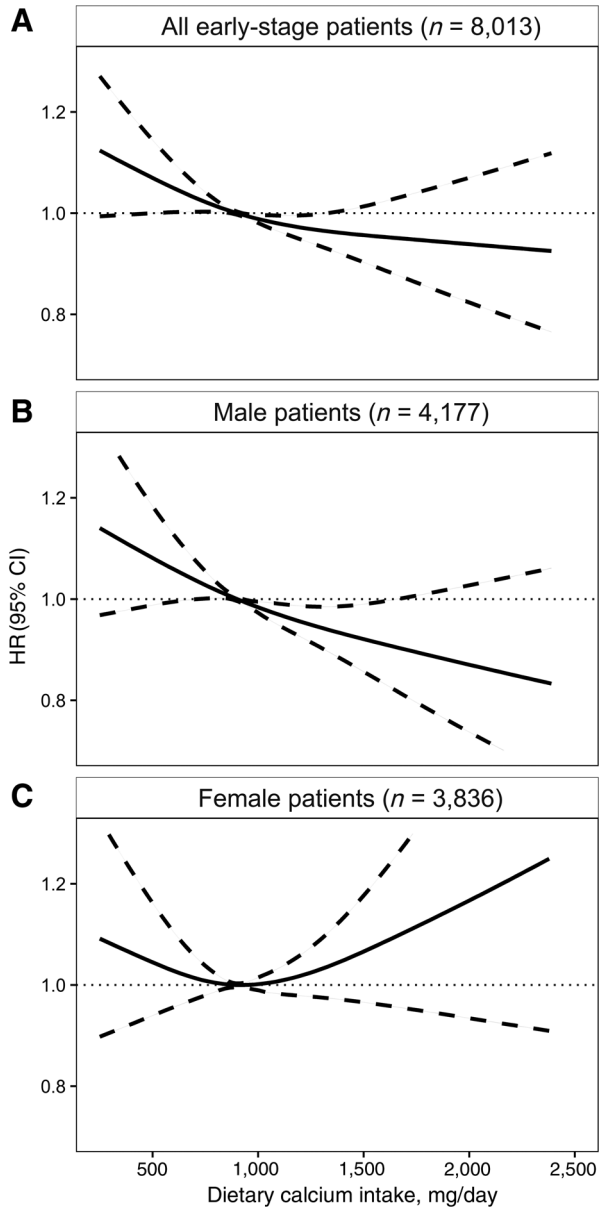

Figure 2.

Risk of death by prediagnostic dietary calcium intake in the Calcium and Lung Cancer Pooling Project (solid line, hazard ratio; dashed line, 95% confidence interval) among **A,** Early-stage lung cancer patients ($P = 0.03$); **B,** Early-stage male patients ($P = 0.02$); and **C,** early-stage female patients ($P = 0.39$). The same stratified, multivariable-adjusted Cox model (Model 2) was used as shown in Table 2 footnote.

individuals would have an insufficient calcium intake when taking calcium supplements. If only a long-term low calcium intake was associated with cancer prognosis, a null association for supplemental calcium would be expected. We did observe a possible trend of beneficial association for supplemental calcium among early-stage patients with low dietary calcium intakes (see Results section). The null finding could also be due to a suboptimal measurement of usual supplement intake. Nevertheless, this finding is in line with results from randomized, controlled trials which found no significant effects of calcium supplements on cancer incidence or mortality (67–69). Taken together, our results support the hypothesis that an optimal calcium intake from foods may favorably impact cancer survival; however, evidence is lacking for a recommendation to use calcium supplements to increase intake, especially among those already consuming a sufficient amount of dietary calcium.

Our study has several limitations. First, dietary intakes were measured via FFQs and food composition tables, both of which have nonnegligible measurement errors. Although FFQs used in participating cohorts have each been validated and shown reasonably good validities (37–45, 47, 48), measurement errors cannot be precluded. Nondifferential misclassifications of calcium intakes may bias our risk ratio estimates toward the null. Second, information on post-diagnostic calcium intake, comorbidity status at the time of diagnosis, and cancer treatment was unavailable, and tumor stage and grade data were missing in a sizable fraction of patients. Cancer treatment and comorbidities may affect calcium homeostasis, which may exacerbate the hazardous effect of a preexisting low calcium status. Lack of treatment and comorbidity information prevented us from investigating this hypothesis. Most of our study patients were diagnosed before 2010 when targeted treatments were less common and lung cancer treatments were largely based on stage, histology, and patient sociodemographics. We adjusted for all these factors, as well as baseline diabetes and obesity status, and stratified by cohort (region) and year of diagnosis. We also conducted a number of subgroup analyses and did not find significant effect modifications except by stage. Moreover, patient tumor characteristics (including the unknown category) were not associated with prediagnostic calcium intake, suggesting that these clinical factors were unlikely to substantially confound the association. Third, despite the large sample size, statistical power remained limited in certain subgroup analyses, such as the interaction analysis by race/ethnicity and the analysis among never smokers. For example, we found a seemingly opposite association in blacks, but the small number of black patients and the insignificant interaction with race/ethnicity prevented us from drawing any conclusions. Finally, we cannot separate the effects of calcium from related nutrients, including vitamin D, magnesium, phosphorus, and other nutrients in calcium-rich foods, nor could we rule out residual confounding from unknown confounders and imperfectly measured covariates, which may be particularly challenging in pooling projects using harmonized data from multiple studies.

Strengths of our study include its prospective design, large sample size, and pooled data analysis. The prospective study design minimized reverse causality and biases of recall and selection. Pooled individual-level data from 12 cohort studies in three continents enabled us to evaluate the associations among populations with a broad range of exposures and by clinical characteristics, and to examine calcium intake via multiple approaches, i.e., using project-wide cutoff points, as continuous variables, and in a series of sensitivity analyses. Results for low dietary calcium intake and poorer survival were largely consistent when using different approaches.

In summary, in this large pooled analysis, we found that low prediagnostic dietary calcium intake (<500–600 mg/d) was associated with a small increased risk of death among localized and regional stage lung cancer patients. Further studies with biomarker data and more detailed clinical data are needed to confirm or

refute our findings. Meanwhile, studies are needed to explore biological mechanisms linking calcium nutrition, calcium homeostasis, and bone remodeling with lung cancer progression, as well as to investigate modifiable nutrition and lifestyle factors to improve survival for lung cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Development of methodology: D. Yu, A. Langhammer, E. Weiderpass, S. Krokstad, X.-O. Shu

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D. Yu, S.A. Smith-Warner, W. Blot, N. Sawada, E. White, N. Freedman, K. Robien, E. Giovannucci, X. Zhang, Y. Park, Y.-T. Gao, R.T. Chlebowski, A. Langhammer, G. Yang, G. Severi, J. Manjer, K.-T. Khaw, E. Weiderpass, S. Krokstad, K. Hveem, R. Sinha, R. Ziegler, S. Tsugane, Y.-B. Xiang, M. Johansson, W. Zheng, X.-O. Shu

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D. Yu, Y. Takata, S.A. Smith-Warner, N. Freedman, X. Zhang, Y. Park, R.T. Chlebowski, E. Weiderpass, Y.-B. Xiang

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