Research Article

Cancer Epidemiology, Biomarkers & Prevention

Mineral Intake and Lung Cancer Risk in the NIH-American Association of Retired Persons Diet and Health Study

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Abstract

Background: Using data from a case-control study, we previously reported that low dietary intakes of magnesium (Mg), iron (Fe), zinc (Zn), copper (Cu), but not selenium (Se) and calcium (Ca), were associated with increased lung cancer risk. Due to dietary recall bias in case-control studies, our objective was to assess whether these findings hold in a prospective cohort study.

Methods: We analyzed data from the NIH-American Association of Retired Persons Diet and Health study of 482,875 subjects (288,257 men and 194,618 women) who were cancer-free and completed a food frequency questionnaire at enrollment between 1995 and 2003. Cox proportional hazards models were computed to estimate the relative risk adjusted for potential confounders.

Results: During a mean follow-up of 7 years, 7,052 lung cancer cases were identified. For all subjects, we observed no significant associations between total (diet + supplement) Ca, Mg, Fe, Cu, Se, and Zn intakes and lung cancer risk. Total Ca intake was protective (P trend < 0.05) for current smokers and subjects with adenocarcinomas. Total Mg intake increased risk (P trend < 0.05) in men and current smokers. Total Fe intake was inversely associated with risk in women (P trend < 0.01). For dietary minerals, Mg increased risk (P trend < 0.05) in all subjects, among men and current smokers. Increased dietary Ca intake reduced risk in women (P trend = 0.05). Dietary Fe decreased risk in all subjects and among women (P trend < 0.05). Mineral intake from supplements did not affect lung cancer risk.

Conclusions: Dietary minerals are risk factors for lung cancer.

Impact: Dietary mineral consumption may influence lung cancer risk, but the associations differ by type of mineral and population subgroups. *Cancer Epidemiol Biomarkers Prev; 19(8); 1976–83. ©2010 AACR.*

Introduction

Lung cancer is the leading cause of cancer deaths in the United States, and despite years of intensive research, the 5-year survival rate is only ~15%. Although cigarette smoking is the leading risk factor, only a fraction of long-term smokers develop lung cancer and roughly 10% to 15% of all lung cancer deaths occur in never smokers (1, 2). Therefore, factors other than cigarette smoke, such as diet, environmental toxicants, and genetics may contribute to lung cancer risk. Using the resources of a large case-control study, we previously reported that low dietary intakes of minerals such as magnesium (Mg), zinc (Zn), copper (Cu), and selenium (Se) are associated with increased lung cancer risk (3, 4). We also reported strong joint effects between dietary intakes of these minerals and DNA repair capacity, with the highest risks in the low Mg, low Zn, and low Cu suboptimal DNA repair capacity groups (4, 5). Because case-control studies of dietary risk factors suffer from recall bias, we used the resources of the large NIH-American Association of Retired Persons (NIH-AARP) prospective cohort study of diet and cancer to validate our previously published findings on mineral intake and lung cancer risk.

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Materials and Methods

Study population

The NIH-AARP Diet and Health prospective cohort study was designed to assess the associations between dietary and environmental risk factors and cancer risk. Details regarding the establishment and recruitment procedures of the NIH-AARP study have previously been published (6). In brief, between October 13, 1995 and May 6, 1996, a questionnaire eliciting information

Table 1. Study participants

(A) Characteristics of participants in the NIH-AARP Diet and Health Study

Variable	No. (%)
Total participants at baseline	482,875
Gender	
Men	288,257 (60)
Women	194,618 (40)
Age, y (men and women combined)	
≤55	65,341 (14)
55–59	109,389 (23)
60–64	135,839 (28)
65–69	155,047 (32)
≥70	17,259 (3)
Ethnicity	
White	441,519 (91)
Black	18,267 (4)
Hispanic	9,061 (2)
Asian	7,866 (2)
Unknown	6,162 (1)
Education	
<8 y	27,752 (6)
8–11 y	93,909 (19)
12 y or completed high school	47,422 (10)
Post-high school or some college	112,048 (23)
College and postgraduate	188,025 (39)
Unknown	13,719 (3)
Smoking status	
Never	170,401 (36)
Former	237,216 (49)
Current	57,142 (12)
Unknown	18,116 (3)
Smoke dose	
Never smoked	170,401 (35)
1–10 cigarettes/d	75,279 (16)
11–20 cigarettes/d	96,372 (20)
21–30 cigarettes/d	58,633 (12)
31–40 cigarettes/d	36,360 (8)
41–60 cigarettes/d	21,746 (5)
≥60 cigarettes/d	5,968 (1)
Unknown	18,116 (3)
Years since quitting smoking (former smokers)	
Stopped ≥10 y ago	176,226 (37)
Stopped 5–9 y ago	33,348 (7)
Stopped 1–4 y ago	19,210 (4)
Stopped within last year	8,432 (2)
Unknown	18,116 (4)
Smoked pipes or cigars regularly for a day or longer	
No	383,355 (80)
Yes, pipes and cigars	35,989 (7)
Yes, pipes only	29,618 (6)
Yes, cigars only	17,873 (4)
Unknown	16,040 (3)

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Table 1. Study participants (Cont'd)

(A) Characteristics of participants in the NIH-AARP Diet and Health Study

Variable	No. (%)
Supplement use	
No	137,827 (29)
Yes	324,142 (67)
Unknown	20,906 (4)
Physical activity	
Never/rarely	83,419 (17)
One to three times per month	65,834 (14)
One to two times per week	104,774 (24)
Three to four times per week	130,547 (27)
Five or more times per week	93,365 (18)
Unknown	4,936 (1)
Lung cancers at follow-up	
Total	7,052
Adenocarcinoma	2,597 (37)
Small cell carcinoma	953 (14)
Squamous cell carcinoma	1,246 (18)
Undifferentiated carcinoma	400 (6)
Lung cancers at follow-up (men)	
Total	4,520
Adenocarcinoma	1,580 (35)
Small cell carcinoma	571 (13)
Squamous cell carcinoma	917 (20)
Undifferentiated carcinoma	260 (6)
Lung cancers at follow-up (women)	
Total	2,532
Adenocarcinoma	1,017 (40)
Small cell carcinoma	382 (15)
Squamous cell carcinoma	329 (13)
Undifferentiated carcinoma	140 (6)

(B) Baseline characteristics of the NIH-AARP Diet and Health Study by age and dietary mineral intakes

Variable	Mean (SD)	Median	Range
Age			
All	62.0 (5.4)	62.6	50.3–71.5
Men	62.2 (5.3)	62.8	50.3–71.5
Women	61.9 (5.4)	62.3	50.3–71.5
Calories (kcal)			
All	1,821.2 (775.8)	1,684.9	322.6–6,125.6
Men	1,999.2 (813.3)	1,861.4	419.1–6,125.6
Women	1,557.4 (630.2)	1,453.3	322.6–4,802.9
Alcohol (g)			
All	12.4 (31.8)	1.9	0–684.8
Men	16.8 (38.8)	3.6	0–684.8
Women	5.9 (16.1)	0.9	0–534.8
Calcium (mg)*			
All	1,001.6 (553.4)	872.8	95.3–5,010.5
Men	946.6 (511.1)	828.4	122.2–4,939.4
Women	1,083.3 (601.5)	961.8	95.3–5,010.5

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Table 1. Study participants (Cont'd)

(B) Baseline characteristics of the NIH-AARP Diet and Health Study by age and dietary mineral intakes

Variable	Mean (SD)	Median	Range
Magnesium (mg)*			
All	374.1 (140.1)	357.2	63.5–1,183.1
Men	394.1 (144.7)	376.5	79.8–1,183.1
Women	344.3 (127.2)	330.9	63.5–1,052.4
Iron (mg)*			
All	23.7 (11.6)	23.2	2.1–84.6
Men	24.5 (11.9)	23.5	2.9–84.6
Women	22.4 (11.2)	22.9	2.1–76.1
Copper (mg)*			
All	2.3 (1.2)	2.2	0.3–8.4
Men	2.4 (1.2)	2.2	0.3–8.4
Women	2.3 (1.2)	2.3	0.3–7.7
Selenium (μg)*			
All	102.3 (43.1)	95.7	12.9–352.4
Men	111.2 (44.9)	104.4	17.8–352.5
Women	89.1 (36.6)	83.9	12.9–287.7
Zinc (mg)*			
All	17.7 (9.3)	17.4	1.6–67.0
Men	18.4 (9.5)	17.4	2.1–67.0
Women	16.7 (8.9)	17.4	1.6–58.3

*Values are for total intake (from diet and supplements).

on dietary intake and health-related behaviors was mailed to 3.5 million members of the AARP, who were ages 50 to 71 years and who lived in eight states in the United States (California, Florida, Georgia, Louisiana, Michigan, New Jersey, North Carolina, and Pennsylvania). Five hundred sixty-six thousand, four hundred and two subjects filled out the baseline questionnaire with satisfactory dietary data. We excluded subjects with cancer at baseline (n = 49,439), proxy respondents (n = 15,760), self-reported end-stage renal disease (n = 769), self-reported poor health (n = 8,366), and those with extreme intakes [more than two times the interquartile ranges of Box-Cox log-transformed total calories (n = 4,314), calcium (n = 1,198), magnesium (n = 516), iron (n = 447), copper (n = 1,522), selenium (n = 819), and zinc (n = 377) from foods]. After exclusions, the analytical cohort consisted of 482,875 participants (n = 288,257 men and n = 194,618 women). The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the U.S. National Cancer Institute.

Follow-up of cohort

As previously described (7), addresses for the NIH-AARP cohort were updated each year by matching the cohort database to that of the National Change of Address database maintained by the U.S. Postal Service. Study participants were followed from enrollment in 1995 to December 31, 2003.

Identification of cancer cases

Incident cases of cancer were identified by linkage of the NIH-AARP cohort membership to eight state cancer registry databases, which have been certified by the North American Association of Central Cancer Registries for meeting the highest standards of data quality. Approximately 90% of cancer cases were detected in the cohort by this approach (7). Cancer sites were identified by anatomic site and histologic code of the International Classification of Disease for Oncology (third edition; ref. 8) as previously described (9).

Dietary and risk factor assessment

The baseline dietary questionnaire has previously been described (6). In brief, dietary intake was assessed by using a validated 124-item food frequency questionnaire, which was an early version of the National Cancer Institute Diet History Questionnaire. Participants were asked to report their usual intake and portion size over the last 12 months, using 10 frequency categories ranging from "never" to "6+ times per day" for beverage intake and from "never" to "2+ times per day" for solid foods and three categories of portion sizes.

Statistical analysis

Person years of follow-up time was calculated from date of the baseline questionnaire until the date of cancer diagnosis, death, moving from registry area, or end of

Table 2. RR of lung cancer by categories of mineral intake, NIH-AARP Diet and Health Study, 1995/1996–2003

	Mineral intake categories					*P* trend
Total Ca (mg/d)	≤608	609–773	774–986	987–1,362	>1,362	
All subjects						
Cases (7,052)	1,770	1,449	1,357	1,242	1,234	
RR*	1.00	1.00 (0.93–1.08)	0.99 (0.92–1.08)	0.92 (0.84–1.01)	0.97 (0.88–1.07)	0.32
Current smokers only						
Cases (2,811)	847	578	515	442	429	
RR*	1.00	0.99 (0.88–1.11)	0.98 (0.86–1.11)	0.83 (0.72–0.96)	0.86 (0.74–1.00)	0.02
Adenocarcinomas only						
Cases (2,597)	623	557	492	475	450	
RR*	1.00	1.03 (0.91–1.17)	0.93 (0.81–1.07)	0.91 (0.78–1.05)	0.87 (0.74–1.02)	0.04
Dietary Ca (mg/d)	≤535	536–641	643–758	759–952	>952	
All subjects						
Cases (7,052)	1,837	1,386	1,272	1,248	1,309	
RR†	1.00	0.94 (0.87–1.02)	0.94 (0.87–1.02)	0.93 (0.85–1.01)	0.92 (0.84–1.01)	0.12
Women only						
Cases (3,621)	809	745	697	670	700	
RR†	1.00	0.89 (0.77–1.01)	0.83 (0.71–0.96)	0.82 (0.71–0.96)	0.82 (0.69–0.97)	0.05
Total Mg (mg/d)	≤296	296–345	346–394	395–448	>449	
All subjects						
Cases (7,052)	1,586	1,432	1,391	1,309	1,334	
RR*	1.00	1.08 (1.00–1.17)	1.07 (0.98–1.17)	1.07 (0.97–1.18)	1.14 (1.01–1.28)	0.07
Men only						
Cases (357)	56	60	102	72	67	
RR*	1.00	1.12 (1.02–1.24)	1.13 (1.01–1.25)	1.15 (1.01–1.30)	1.21 (1.04–1.41)	0.02
Current smokers only						
Cases (2,811)	730	615	531	468	467	
RR*	1.00	1.19 (1.06–1.34)	1.07 (0.93–1.22)	1.11 (0.95–1.30)	1.28 (1.06–1.54)	0.04
Dietary Mg (mg/d)	≤273	273–306	307–336	337–376	>376	
All subjects						
Cases (7,052)	1,628	1,416	1,288	1,370	1,350	
RR†	1.00	1.09 (1.01–1.18)	1.07 (0.98–1.16)	1.15 (1.05–1.26)	1.16 (1.04–1.30)	<0.01
Men only						
Cases (357)	65	80	70	69	73	
RR†	1.00	1.09 (0.99–1.20)	1.10 (0.99–1.22)	1.21 (1.08–1.35)	1.19 (1.03–1.36)	<0.01
Current smokers only						
Cases (2,811)	777	568	496	491	479	
RR†	1.00	1.10 (0.97–1.24)	1.12 (0.98–1.27)	1.16 (1.00–1.33)	1.22 (1.02–1.44)	0.02
Total Fe (mg/d)	≤13.39	13.40–17.43	17.44–28.68	28.69–33.20	>33.20	
All subjects						
Cases (7,052)	1,769	1,360	1,325	1,423	1,175	
RR*	1.00	1.00 (0.93–1.09)	0.91 (0.83–1.00)	0.95 (0.83–1.09)	0.87 (0.73–1.03)	0.20
Women only						
Cases (3,621)	815	675	750	713	668	
RR*	1.00	0.98 (0.86–1.11)	1.01 (0.88–1.16)	0.83 (0.71–0.98)	0.79 (0.65–0.97)	<0.01
Dietary Fe (mg/d)	≤11.89	11.90–13.47	13.48–15.24	15.25–17.81	>17.81	

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Table 2. RR of lung cancer by categories of mineral intake, NIH-AARP Diet and Health Study, 1995/1996–2003 (Cont'd)

	Mineral intake categories					*P* trend
All subjects						
Cases (7,052)	1,953	1,423	1,373	1,214	1,089	
RR†	1.00	0.99 (0.91–1.07)	1.04 (0.96–1.13)	0.98 (0.89–1.07)	0.87 (0.79–0.97)	0.02
Women only						
Cases (3,621)	815	675	750	713	668	
RR†	1.00	0.98 (0.86–1.11)	1.01 (0.88–1.16)	0.83 (0.71–0.98)	0.79 (0.65–0.97)	<0.01

NOTE: We do not show data for the intakes of selenium, copper, and zinc due to space limitations and because these associations were null across the board.

*Models for total dietary intake: adjusted for age (continuous), sex, race/ethnicity, education, cigarette smoke dose, smoke quit, body mass index (continuous), physical activity, alcohol intake (continuous), and food calories + total other minerals (diet + supplement).

†Models for dietary intake only: model adjusted for age (continuous), sex, race/ethnicity, education, cigarette smoke dose, smoke quit, body mass index (continuous), physical activity, alcohol intake (continuous), and food calories (continuous) + all other dietary minerals + supplement use (yes/no).

follow-up (December 31, 2003), whichever occurred first. Dietary minerals were energy-adjusted by the residual method (10). Age-adjusted and multivariable Cox proportional hazards models (11) were computed to estimate relative risks (RR) and 95% confidence intervals for each quintile of mineral intake (total intake, dietary intake, and intake from supplements) compared with the lowest quintile. Total intake for each mineral was computed by summing the energy-adjusted intake and the raw supplemental intake. Due to the significant correlations between the intake of dietary minerals, in our models, we mutually controlled for other minerals. The covariates chosen for inclusion in the multivariate model were based on previously identified risk factors for lung cancer. We also conducted subgroup analyses by gender, smoking status, and lung cancer histology. All the values presented were two-sided and $P < 0.05$ was considered statistically significant.

Results

There were a total of 482,875 subjects (~60% men) at baseline and the age range was between 50 and 71 years in both men and women. About 91% (441,752) were non-Hispanic whites. About 23% of the population had post-high school or some college education and ~39% had college and postgraduate education. Most participants were former smokers (237,216 or 49%); 170,401 (35%) were never smokers; 57,142 (12%) were current smokers, whereas smoking status was unknown in 18,116 (4%) participants. About 67% took some form of supplement whereas 28% reported never using supplements. During the mean follow-up of 7 years, from 1995 to 2003, a total of 7,052 lung cancer cases were identified (4,520 in men and 2,532 in women). Of the 7,052 lung cancer cases, 2,579 (37%) were adenocarcinomas, 1,246 (18%) were squamous cell carcinomas, 953 (14%) were small cell carcinomas, and 400 (6%) were undifferentiated carcinomas (Table 1A).

The mean total (diet + supplement) intake was as follows: Ca, 1,002 mg/d (men, 947 mg/d; women, 1,083 mg/d); Mg, 374 mg/d (men, 394 mg/d; women, 344 mg/d); Fe, 24 mg/d (men, 24 mg/d; women, 22 mg/d); Cu, 2.32 mg/d (men, 2.37 mg/d; women, 2.25 mg/d); Se, 102 μg/d (men, 111 μg/d; women, 89 μg/d); and Zn, 17.7 mg/d (men, 18.4 mg/d; women, 16.7 mg/d). The values for men and women are also reported in Table 1B.

Overall, we found no significant associations between total (diet + supplement) Ca, Fe, Cu, Se, and Zn intakes and lung cancer risk (Table 2; data not shown for Cu, Se, and Zn because no significant associations were found).

In subgroup analysis, for total mineral intake, among current smokers, only total Ca intake was inversely and significantly associated with risk. Similar risk reductions were observed for increased total Ca intake among cases with adenocarcinomas. For total Fe intake in women, the highest quintile of total intake was associated with a 21% reduction in risk.

Dietary Ca intake had a null effect in the total population. However, among women, it significantly reduced lung cancer risk ranging from 11% to 18% (Table 2). A borderline trend for increased risk with increasing total Mg intake was observed with a significant 14% increased risk in the highest quintile of intake. In stratified analyses, significant trends for direct associations between total Mg intake and lung cancer risk were seen for men and

current smokers. Specifically, men in the highest quintile of intake had a 21% increased risk whereas current smokers had a 28% higher risk. Dietary intake of Mg was similarly associated with increased risk overall in men and current smokers. Overall, for dietary Fe, the highest quintile of intake was associated with a significant 13% reduced risk (Table 2). Similar results were found for women only. We did not find any associations between mineral (Ca, Mg, Fe, Cu, Se, and Zn) intake from supplements and lung cancer risk.

Discussion

Overall, we found no evidence that total (dietary + supplement) intake of Ca, Fe, Cu, Se, or Zn was associated with lung cancer risk. For dietary minerals separately, null associations were found for dietary Ca intake, but dietary Mg showed a trend for increased risk ($P < 0.01$) whereas dietary Fe trended to reduce risk ($P = 0.02$). Because non-Hispanic whites (91% of the population) may have different dietary habits than non-whites, we restricted our analysis to non-Hispanic whites only and the results did not change. To our knowledge, this is the first report of a prospective analysis of dietary intake of Mg and Cu on lung cancer risk.

Subgroup analyses revealed increased total Ca intake reduced lung cancer risk in current smokers (2,811 cases) and was protective against adenocarcinomas (2,597 cases). Dietary Ca intake was protective for women (3,621 cases) only. For dietary Mg intake, increased risks were also seen in men (357 cases) and current smokers (2,811 cases). Similarly, dietary Fe intake reduced risk in women (3,621 cases). These are biologically plausible findings, but one cannot rule out chance. For example, Ca is a mediator of reactive oxygen species (12) and increasing levels of Ca^{2+} in the cytoplasm lead to influx into the mitochondria and nuclei, which could affect DNA stability (12) and lung cancer risk. Also, Fe is required for cellular function, but Fe overload might generate reactive oxygen species and damage DNA (13). Dietary Fe overload would not be expected among women (age range, 50–71 years) in the study.

In an analysis of the top 25 food contributors to Ca, Mg, Fe, Cu, Zn, and Se, no single food was a major contributor to any of these mineral in the diet, rather, various foods contributed small amounts of these minerals, with significant intercorrelations among them. In our study, at baseline, the population consumed daily amounts of dietary Ca, Mg, Fe, Cu, Zn, and Se comparable with the values reported by the National Health and Nutrition Examination Survey (1999–2000) for the United States population (14).

Our findings do not support our previous results from a large case-control study showing that increased dietary intake of minerals such as Mg, Zn, and Cu were associated with lower lung cancer risk (3-5). Our results also do not support reports from other case-control studies showing that higher intakes of dietary Se (15) and Zn (16) decreased lung cancer risk. In the Women's Health Initiative cohorts, multivitamin use was not associated with lung cancer risk (17). However, in a secondary analysis of the Nutritional Prevention of Cancer trial, Se supplementation significantly reduced lung cancer risk by 46% (18, 19). In the recent Selenium and Vitamin E Cancer Prevention Trial, the Se supplementation group was not associated with lung cancer risk (20). In addition, higher serum Se levels were not associated with lung cancer risk in a case-control study nested within the Multiethnic Cohort Study (21). One reason why the current study does not support the findings from our previous case-control study (3-5) might be recall bias. Cases might recall their diet differently from healthy controls and might change their dietary habits after symptoms appear. The NIH-AARP cohort did not include Texas, the location for our case-control study, in which dietary habits and mineral context of the soil may be different from states where the cohort participants reside. In our study, we rigorously accounted for smoking status, smoke dose, and years since quitting smoking, but still could not rule out whether smoking inherently confounded the dietary effects.

Study limitations might have affected the current results. Although we adjusted for potential risk factors available in our study for lung cancer, residual confounding may exist. Residual confounding could account for weak associations because smoking is clearly a strong risk factor for lung cancer, is likely related to some dietary factors, and diet might not be perfectly measured. Using energy as a covariate as an alternative to using residuals did not change the results. Another common concern is the significant collinearity among the minerals. Despite the high correlations, our results show that all minerals did not have similar effects on lung cancer risk. Our models incorporate simultaneous adjustment for other minerals as covariates.

Also, the food frequency questionnaire, although practical for large epidemiology studies, has been associated with measurement errors. Although the food frequency questionnaire used in the NIH-AARP study has been validated, the accuracy of intake of the wide range of nutrients is always a concern because the mineral values of foods in the food composition database might be based on laboratory techniques no longer considered accurate and on insufficient samples of foods for precision around the value. Furthermore, diet and supplement intake were assessed once at baseline and might not reflect long-term intake as would be expected from repeated assessments of diet during the follow-up period.

Our observations need confirmation, including the unexpected results that dietary Mg intake might increase lung cancer risk because Mg was thought to protect against lung cancer through its role in maintaining genetic stability (22), regulation of cell proliferation (23), and

protection against inflammation (24). Future studies of dietary minerals and lung cancer risk need to carefully consider measurement error issues and confounding from smoking.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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