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Mineral intake and lung cancer risk in the NIH-AARP 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-AARP 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 (FFQ) at enrollment between 1995 and 2003. Cox proportional hazards models were computed to estimate the relative risk (RR) 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 mineral consumption may influence lung cancer risk, but the associations differ by type of mineral and population subgroups.

Keywords

Diet; minerals; lung cancer; smoking

Introduction

Lung cancer is the leading cause of cancer deaths in the US, and despite years of intensive research the 5-year survival rate is only about 15%. While cigarette smoking is the leading

risk factor, only a fraction of long-term smokers develops lung cancer and roughly 10–15% 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 (DRC), with the highest risks in the low Mg-, low Zn-, and low Cu-suboptimal DRC groups (4,5). Since case-control studies of dietary risk factors suffer from recall bias, we used the resources of the large NIH-AARP prospective cohort study of diet and cancer to validate our previously published findings on mineral intake and lung cancer risk.

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 Oct 13, 1995 and May 6, 1996, a questionnaire eliciting information on dietary intake and health-related behaviors was mailed to 3.5 million members of AARP, who were aged 50–71 years and who lived in eight states in the USA (California, Florida, Georgia, Louisiana, Michigan, New Jersey, North Carolina and Pennsylvania). 566,402 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 (beyond two times the inter-quartile 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 (NCI).

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 US Postal Service. Study participants were followed from enrollment in 1995 through to December 31, 2003.

Identification of cancer cases

Incident cases of cancer were identified by linkage of the NIH-AARP cohort membership to 8 state cancer registry databases, which have been certified by the North American Association of Central Cancer Registries (NAACCR) 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 (ICD-O, third edition) (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 (FFQ), which was an early version of the NCI 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 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 (RRs) and 95% confidence intervals (95% CI) for each quintile of mineral intake (total intake, dietary intake, and intake from supplements) compared with the lowest quintile (Table 2). 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 (see footnote to Table 2). The covariates chosen for inclusion in the multivariate model were based on previously identified risk factors for lung cancer (see footnote to Table 2). We also conducted sub-group analyses by gender, smoking status, and lung cancer histology. All the values presented are two-sided and $P < 0.05$ was considered statistically significant.

Results

There were a total of 482,875 subjects (approximately 60% men) at baseline and the age range was between 50–71 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 about 39% had college and post-graduate education. Most participants were former smokers (237,216 or 49%); 170,401 (35%) were never smokers; 57,142 (12%) were current smokers, while 18,116 (4%) smoking status was unknown. About 67% took some form of supplement whereas 28% reported never using supplements. During the mean follow-up of 7 years, from 1995 through 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%) squamous cell carcinomas, 953 (14%) small cell carcinomas, and 400 (6%) 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/day (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, Zn since 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 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 analysis, 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, 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 ($P<0.01$) while dietary Fe trended to reduce risk ($P=0.02$). Since 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 (2811 cases) and was protective against adenocarcinomas (2597 cases). Dietary Ca intake was protective for women (3621 cases) only. For dietary Mg intake, increased risks were also seen in men (357 cases) and current smokers (2811 cases). Similarly dietary Fe intake reduced risk in women (3621 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 may 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 the top 25 food contributors to Ca, Mg, Fe, Cu, Zn, Se no single food was a major contributor to any of these mineral in the diet, rather various foods contribute small amounts of these minerals, with significant inter-correlations among them. In our study, at baseline the population consumed comparable daily amounts of dietary Ca, Mg, Fe, Cu, Zn, and Se to values reported by the National Health and Nutrition Examination Survey (NHANES), 1999–2000, for the US 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 secondary analysis of the nutritional prevention of cancer (NPC) trial, Se supplementation significantly reduced lung cancer risk by 46% (18,19). In the recent Se and vitamin E cancer prevention trial (SELECT), 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 do not support the findings from our previous case-control study (3–5) may be recall bias. Cases may recall their diet differently from healthy controls and may change their dietary habits after symptoms appear. The NIH-AARP cohort did not include Texas, the location for our case-control study where

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 quit smoking, but still cannot rule out whether smoking inherently confounded the dietary effects.

Study limitations may 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 since smoking is clearly a strong risk factor for lung cancer, is likely related to some dietary factors, and diet may 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 demonstrate that all minerals did not have similar effects on lung cancer risk. Our models incorporate simultaneous adjustment for other minerals as covariates.

Also, the FFQ, although practical for large epidemiology studies, has been associated with measurement errors. While the FFQ used in the NIH-AARP study has been validated, accuracy of intake of the wide range of nutrients is always a concern because the mineral values of foods in the food composition database may be based on laboratory techniques no longer considered accurate and insufficient samples of foods for precision around the value. Further, diet and supplement intake were assessed once at baseline and may 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 may 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.

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Table 1a

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

Variable	Number (%)
Total participants at baseline	482,875
<i>Gender</i>	
Men	288,257 (60)
Women	194,618 (40)
<i>Age (men and women combined)</i>	
≤ 55 yrs	65,341 (14)
55–59 yrs	109,389 (23)
60–64 yrs	135,839 (28)
65–69 yrs	155,047 (32)
≥ 70 yrs	17,259 (3)
<i>Ethnicity</i>	
White	441,519 (91)
Black	18,267 (4)
Hispanic	9,061 (2)
Asian	7,866 (2)
Unknown	6,162 (1)
<i>Education</i>	
less than 8 years	27,752 (6)
8–11 years	93,909 (19)
12 years or completed high school	47,422 (10)
post-high school or some college	112,048 (23)
college and post graduate	188,025 (39)
unknown	13,719 (3)
<i>Smoking Status</i>	
Never	170,401 (36)
Former	237,216 (49)
Current	57,142 (12)
Unknown	18,116 (3)
<i>Smoke Dose</i>	
Never smoked	170,401 (35)
1–10 cigarettes a day	75,279 (16)
11–20 cigarettes a day	96,372 (20)
21–30 cigarettes a day	58,633 (12)
31–40 cigarettes a day	36,360 (8)
41–60 cigarettes a day	21,746 (5)
≥ 60 cigarettes a day	5,968 (1)
Unknown	18,116 (3)

Variable	Number (%)
<i>Years since quit smoking (former smokers)</i>	
Stopped 10 or more years ago	176,226 (37)
Stopped 5–9 years ago	33,348 (7)
Stopped 1–4 years ago	19,210 (4)
Stopped within last year	8,432 (2)
Unknown	18,116 (4)
<i>Smoked pipes or cigars regularly for a day or longer</i>	
No	383,355 (80)
Yes, pipes & cigars	35,989 (7)
Yes, pipes only	29,618 (6)
Yes, cigars only	17,873 (4)
Unknown	16,040 (3)
<i>Supplement use</i>	
No	137,827 (29)
Yes	324,142 (67)
Unknown	20,906 (4)
<i>Physical activity</i>	
Never/Rarely	83,419 (17)
1–3 times per month	65,834 (14)
1–2 times per week	104,774 (24)
3–4 times per week	130,547 (27)
5 or more times per week	93,365 (18)
Unknown	4,936 (1)
<i>Lung cancers at follow-up</i>	
Total	7,052
Adeno carcinoma	2,597 (37)
Small cell carcinoma	953 (14)
Squamous cell carcinoma	1,246 (18)
Undifferentiated carcinoma	400 (6)
<i>Lung cancers at follow-up (Men)</i>	
Total	4,520
Adeno carcinoma	1,580 (35)
Small cell carcinoma	571 (13)
Squamous cell carcinoma	917 (20)
Undifferentiated carcinoma	260 (6)
<i>Lung cancers at follow-up (Women)</i>	
Total	2,532
Adeno carcinoma	1,017 (40)
Small cell carcinoma	382 (15)

Variable	Number (%)
Squamous cell carcinoma	329 (13)
Undifferentiated carcinoma	140 (6)

Table 1b

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
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).

Table 2

Relative risk 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	987–1362	>1362	
All subjects						
Cases (7052)	1770	1449	1357	1242	1234	
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 (2811)	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 (2597)	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 (7052)	1837	1386	1272	1248	1309	
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 (3621)	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 (7052)	1586	1432	1391	1309	1334	
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 (2811)	730	615	531	468	467	

	Mineral intake categories						P-trend
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		
<i>All subjects</i>							
Cases (7052)	1628	1416	1288	1370	1350		
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
<i>Men only</i>							
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
<i>Current smokers only</i>							
Cases (2811)	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		
<i>All subjects</i>							
Cases (7052)	1769	1360	1325	1423	1175		
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
<i>Women only</i>							
Cases (3621)	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		
<i>All subjects</i>							
Cases (7052)	1953	1423	1373	1214	1089		
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
<i>Women only</i>							
Cases (3621)	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

RR – Relative risk

[†] **Models for total dietary intake:** Adjusted for age (continuous), sex, race/ethnicity, education, cigarette smoke dose, smoke quit, BMI (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, BMI (continuous), physical activity, alcohol intake (continuous) and food calories (continuous) + all other dietary minerals + supplement use (yes/no)

^{††}**Models for dietary supplements only:** Adjusted for age (continuous), sex, race/ethnicity, education, cigarette smoke dose, smoke quit, BMI (continuous), physical activity, alcohol intake (continuous) and food calories (continuous) + all other single supplements (for example supplemental calcium there is mutual adjustment for supplement copper, iron magnesium, zinc, and selenium).

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