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Association of combined mineral intakes with risk of incident, sporadic colorectal adenoma

By

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Degree to be awarded: Master of Public Health

Epidemiology

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Abstract Cover Page

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MBBS
Dr. NTR University of Health Sciences
2013

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An abstract of
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Abstract

Association of combined mineral intakes with risk of incident, sporadic colorectal adenoma

By Tapasya Raavi

There are few reported epidemiologic studies on associations of mineral intakes other than calcium, with colorectal neoplasms, and just one of those studies investigated multiple minerals in aggregate. In the latter study, a higher mineral score was statistically significantly inversely associated with incident colorectal cancer. We incorporated 8 minerals into a mineral intake score and investigated its association with incident, sporadic colorectal adenomas, using pooled data from three case-control studies (n = 779 cases, 2,026 controls) conducted in Minnesota, North Carolina, and South Carolina. Participants' mineral intakes were expressed as nutrient densities and categorized according to their distributions among the controls. Total (dietary plus supplemental) calcium, magnesium, zinc, and potassium intake quintiles were assigned scores of 1 – 5, with higher ranks indicating higher, potentially anti-colorectal carcinogenic intakes, whereas iron, copper, phosphorus, and sodium intake quintiles were assigned scores in the reverse order to account for their possible pro-colorectal carcinogenic properties. The rankings were summed to create participants' mineral scores, and the association of the score with incident, sporadic colorectal adenomas was estimated using multivariable unconditional logistic regression. The multivariable-adjusted odds ratios (OR) for the mineral score-adenoma association were close to null (e.g., the OR for those in the highest relative to the lowest score quintile was 1.05 (95% confidence interval 0.81, 1.37]). Our findings suggest that higher calcium, magnesium, zinc, and potassium intakes, combined with lower iron, copper, phosphorus, and sodium intakes may not be associated with incident, sporadic colorectal adenoma risk.

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Association of combined mineral intakes with risk of incident, sporadic colorectal adenoma

Introduction

Colorectal cancer is the second most common cause of cancer related deaths among men and women combined in the US (1). The colorectal adenomatous polyp (adenoma), a benign neoplasm, is the immediate precursor to most colorectal cancers (2), and diet and lifestyle factors have been similarly associated with both colorectal cancer and adenomas (3,4). Calcium has been consistently inversely associated with colorectal neoplasms across multiple observational studies (5–7). As summarized in Table 1, there is considerable biological plausibility for minerals other than calcium (magnesium, zinc, potassium, iron, copper, phosphorus, and sodium) affecting risk for colorectal neoplasms. However, relatively fewer studies have reported on associations of these other minerals with colorectal neoplasms.

We hypothesize that, although the contributions of individual minerals to colorectal adenoma risk may be small, collectively they may be substantial. Importantly, the individual minerals may interact with one another in ways that may affect risk. Several minerals biologically interact with one another; as examples copper competes with zinc and iron, and calcium competes with magnesium for intestinal absorption and transport (7–9). Other examples include the requirement of balanced levels of copper and zinc for the proper functioning of copper-zinc superoxide dismutase, an anti-oxidation enzyme with tumor suppressive properties (8), and the requirement of a copper-dependent ferroxidase protein, Hephaestus, for dietary iron transport (9). Dietary scores are

increasingly used to account for the possible combined effects of multiple, often correlated and interacting dietary exposures (10).

The associations of specific minerals, other than calcium, with risk for colorectal neoplasms were investigated in very few studies. Only one study, a prospective cohort study, investigated an association of multiple mineral intakes combined into a mineral intake score, finding it to be statistically associated with risk (11). To our knowledge, there are no reported investigations of a mineral score-colorectal adenoma association. Accordingly, we investigated an association of intakes of calcium, magnesium, zinc, potassium, iron, copper, phosphorus, and sodium combined into a mineral intake score, with risk for incident, sporadic colorectal adenomas in a pooled case-control study.

Materials and Methods

Study Population

Data were pooled from three colonoscopy-based case-control studies of incident, sporadic colorectal adenoma, the Minnesota Cancer Prevention Research Unit Case-Control Study (CPRU), and the Markers of Adenomatous Polyps studies I (MAP I) and II (MAP II). These studies were conducted in three different states in the US, and patients were recruited using identical subject recruitment and data collection protocols. The recruited patients were scheduled for outpatient, elective colonoscopy by community gastroenterology practices. In the CPRU study, two additional sets of controls were recruited: 1) patients being screened using flexible sigmoidoscopy in the same community practices as the colonoscopy-based controls (patients had a subsequent

colonoscopy if found to have a polyp on sigmoidoscopy), and 2) persons randomly selected from the community in the Minneapolis–St. Paul metropolitan region as previously described (12). For all subjects, self-reported data, including lifestyle, dietary, and medical history, were collected before case or control status was determined. Similar eligibility criteria were used for all studies, which included 35–74 year-old English-speaking subjects with no known history of inflammatory bowel disease, colorectal adenoma, or cancer (excluding non-melanoma skin cancer), and no genetic syndromes associated with colonic neoplasia. Cases were defined as subjects with first ever pathology-confirmed adenoma(s) at colonoscopy, while controls were those without any polyps found at colonoscopy (all studies) or sigmoidoscopy (CPRU), and the CPRU community controls with no reported history of colorectal neoplasms. For the purpose of our pooled analysis, we combined cases from all three studies into one case group, and all controls into one control group. The initial sample sizes of each study were: 574 cases and 707 colonoscopy, 538 sigmoidoscopy, and 550 community controls combined as one control group for CPRU; 184 cases and 236 colonoscopy controls for MAP I; and 49 cases and 154 colonoscopy controls for MAP II. Subjects were excluded from this pooled analysis if their total energy intake estimated from the self-reported Willett semi-quantitative food frequency questionnaire (FFQ) was <600 or >6,000 kilocalories per day, or if more than 10% of their FFQ data were missing. The final sample size for this pooled case-control study was 779 incident, sporadic adenoma cases and 2,026 controls. From the above-noted FFQ, mineral intakes were assessed as total, dietary, and supplemental intakes.

Mineral score components and their assessment

The food and supplement data derived from FFQs were used to calculate mineral scores for all participants. Table 1 lists the 8 components of the mineral score, the rationale behind their inclusion, and the predominant sources of these minerals. For most mineral intakes, we summed the values derived from both dietary intakes and supplements. Nutrient density intakes were calculated as the intake of a mineral per 1,000 kilocalories of total energy intake per day, and then the intakes of each mineral were categorized into quintiles based on the distribution within the controls. For each mineral hypothesized to reduce colorectal cancer risk, each subject was assigned a value equal to their quintile rank (i.e., a value of 1 – 5, with lower ranks indicating lower mineral intakes and higher ranks indicating higher mineral intakes). For each mineral hypothesized to have predominantly pro-carcinogenic properties in the colon, the values assigned to the rankings were reversed (i.e., values of 5 – 1, with lower ranks indicating higher mineral intakes and higher ranks indicating lower mineral intakes). Finally, each participant's values for each mineral were summed to represent their mineral score; thus, the range of possible scores was 8 – 40.

Statistical analysis

All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). All P-values were two-sided, and a P-value <0.05 or a 95% confidence interval that excluded 1.0 was considered statistically significant. Selected participant characteristics at baseline among cases and controls were summarized and compared using Pearson's chi-square and Fisher's exact tests for categorical variables and the Student t-test for continuous variables. The association of the mineral score—as a

continuous variable and categorized according to quintiles based on the study- and sex-specific distributions among the controls—with risk of incident, sporadic, colorectal adenoma was estimated using multivariable logistic regression to calculate odds ratios (OR) and their 95% confidence intervals (95% CI). The potential covariates were chosen a priori as previously having been found to be strong risk factors for colorectal adenoma. Criteria for inclusion in the final models were plausibility, previous literature, and whether inclusion or exclusion in the model changed the estimate for the mineral score by ≥ 10%. Initial models were adjusted for study, age, sex, and total energy intake, and the final full models were additionally adjusted for regular aspirin or NSAID use, family history of colorectal cancer, total fat intake (energy adjusted). A test for trend was calculated using the median value for each quintile of the mineral score.

The analyses were also repeated separately for different colorectal adenoma sites, degree of atypia —mild/>mild, size —<1cm/≥1cm, shape — pedunculated/sessile, and subtype — tubular/tubulovillous and villous, based on the characteristics of the largest adenoma. Incident adenomas in the cecum, appendix, ascending colon, hepatic flexure, and transverse colon were categorized as proximal colorectal adenomas, and adenomas in the splenic flexure, descending colon, sigmoid colon, rectosigmoid junction, and rectum were categorized as distal colorectal cancer.

The above models were also applied in stratified analyses, which were conducted to examine the association of the mineral score with colorectal adenoma according to categories of selected covariates. Strata for continuous variables, such as age, were created based on values above and below the population median. Strata for categorical

variables were as follows: sex—male/female; family history of colorectal cancer in a first degree relative—yes/no; regular use of aspirin or nonsteroidal anti-inflammatory drugs—yes/no; total fat intake (energy adjusted)—low/high; and total vitamin E intake —low/high.

We also conducted several sensitivity analyses. The first set of sensitivity analyses was to investigate whether mineral sources (foods vs. supplements), mineral category (putatively anti- vs. pro-carcinogenic), or any individual score component was particularly influential in the observed associations. We created separate supplement-only and diet-only mineral scores, and categorized the two scores into tertiles and quintiles respectively, and assessed their joint/combined association with colorectal adenoma. Similarly, we created separate anti- and pro-carcinogenic mineral scores, assessed their correlation with Pearson correlation coefficients, and then categorized the two scores into tertiles and assessed their joint/combined association with colorectal adenoma. For the latter analysis, participants with a joint low anti-carcinogenic mineral score/high pro-carcinogenic mineral score were chosen as the reference category. Last, we took individual mineral components in and out of the mineral score one at a time and assessed the associations of a) the remaining 7-component scores with colorectal adenoma, and b) each mineral score component individually with colorectal adenoma, adjusted for its respective remaining 7-component mineral score.

Results

Selected baseline characteristics of study subjects are presented in Table 2. Cases on an average, were 4 years older, and were more likely to be male, current smokers, and

not regularly take an NSAID. Cases also had a slightly higher mean BMI and WHR, and on an average, consumed more total energy, total fat, total meat, and alcohol. Cases also had a slightly higher BMI and waist–hip ratio.

Multivariable-adjusted associations of mineral intake scores with incident, sporadic colorectal adenomas are presented in Table 3. Adjustment for multiple known and suspected risk factors had a minimal effect on the risk estimates. In the multivariable-adjusted analyses, when analyzed by quintiles, there was no pattern for increasing/decreasing adenoma risk with an increasing mineral intake score, nor when comparing those in the highest to the lowest mineral intake score quintiles. The separate findings for total and supplemental mineral intakes were also closer to null and not statistically significant. There were no substantial or consistent differences in our findings across categories of age, sex, family history of colorectal cancer in a first degree relative, total fat intake and total vitamin E intake (Table 4), or for adenomas with different characteristics (Table 5).

In the multivariable-adjusted joint/combined associations of anti-carcinogenic and pro-carcinogenic components of the mineral score with incident colorectal adenoma (Table 6), there was a decreasing risk of adenoma with an increasing anti-carcinogenic mineral score for any given tertile of the pro-carcinogenic mineral score, but the least risk was not among those who were in the joint high anti-carcinogenic/low pro-carcinogenic mineral score category relative to the reference group.

Our sensitivity analyses: The joint/combined analysis of the diet-only and supplement-only mineral scores did not reveal any conclusive or statistically significant

findings (Supplement Table 1). The risk estimates with removal/replacement of each score component one at a time (Supplement Table 2) differed minimally from those with the full score. The associations of each individual mineral with the risk of adenoma, adjusted for its respective remaining 7-component mineral score, are shown in Supplementary Table 3. The estimated associations for calcium, magnesium, and potassium were all close to null but were in the inverse directions (ORs for those in the upper relative to the lower quintile: 0.98, 0.96, 0.89, respectively, none of which was statistically significant), but the estimate for zinc was slightly direct (OR 1.04; 95% CI 0.76, 1.44). The estimated association for phosphorus was close to null, but slightly direct (OR 1.04) and not statistically significant. The OR for sodium was strongly direct and statistically significant (OR 1.50; 95% CI 1.21, 2.01), and, unexpectedly, the estimated associations for copper and iron were inverse and statistically significant (OR 0.68; 95% CI 0.49, 0.94), and (OR 0.65; 95% CI 0.48, 0.91), respectively. The Pearson correlation coefficient for the correlation between the putative pro-carcinogenic and the anti-carcinogenic mineral scores was 0.74. Pearson correlation coefficients for correlations among the individual score components are shown in (Supplementary Table 4). Putatively anti-carcinogenic magnesium and potassium were highly positively correlated with putatively pro-carcinogenic copper, phosphorus, and sodium, and, as expected, calcium was highly correlated with phosphorus.

Discussion

Our study results do not suggest an association of our combined mineral intake score with risk of incident, sporadic colorectal adenoma, overall or within categories of

age, sex, fat and energy intakes, or a family history of colorectal cancer in a first degree relative. Our findings are not consistent with much of the data available from previous studies on several of these individual mineral intakes with risk of colorectal neoplasms. The anti-colon carcinogenic effects of calcium, magnesium, zinc, potassium, and the pro-colon carcinogenic effects of iron, copper, phosphorus, and sodium are not supported by our findings.

To our knowledge, there has been just one previous report on the association of combined intakes of the aforementioned 8 minerals with colorectal neoplasms. Swaminath et al, reported a statistically significant, approximately 25% lower risk of colorectal cancer among those in the upper relative to the lowest mineral score quintile (11). However, Swaminath et al., investigated an association of a combined mineral intake with colorectal cancer, a more downstream endpoint in the process of colon carcinogenesis. Taken together, the findings suggest that any possible effects of combined mineral intakes on risk may be more pronounced in the later stages of colorectal pathogenesis. On the other hand, there were some methodological differences in the conduct of these two studies. Our study included fewer minerals for creating the score, as the mineral intake data was not uniform across the 3 pooled case-control studies. Also, in our study the pro-carcinogenic and anti-carcinogenic minerals were so highly correlated that their effects could have cancelled each other out. It is also possible that there were not enough people who were truly high in one group combined with being truly low in the other.

The role of calcium in relation to colorectal neoplasms has been extensively investigated, whereas the possible roles of other minerals in relation to the disease have been relatively less studied. In a 2016 meta-analysis of four randomized, controlled trials on the efficacy of supplemental calcium on reducing colorectal adenoma recurrence, the summary relative risk (RR) was 0.89 (95% CI, 0.82-0.96) (13). In a 2016 meta-analysis of 8 case-control and 2 prospective cohort studies of an iron-colorectal adenoma association, the summary of the RRs for those in the highest relative to the lowest categories of intakes of total iron (dietary plus supplemental), dietary iron, supplemental iron, and heme iron were, respectively, 0.93 (95% CI, 0.62-1.42), 0.83 (95% CI, 0.71-0.98), 0.73 (95% CI, 0.54-0.97), and 1.23 (95% CI, 1.03-1.48) (14). In a French-based prospective study (n = 67,3112, of whom 172 developed colorectal carcinoma or carcinoma), the RR for those in the fourth relative to the first quartile of phosphorus intake was 0.70 (95% CI, 0.54-0.90) (15). To the best of our knowledge, there are no reported studies on the associations of potassium, or sodium intakes with colorectal neoplasms.

A few studies investigated associations of limited combinations of certain minerals with colorectal neoplasms. In a case-control study (n = 688 adenoma cases, 1,306 polyp-free controls), total magnesium consumption was statistically significantly inversely associated with colorectal adenoma, primarily among individuals with a low calcium:magnesium intake ratio (16). In another pooled case-control study of colorectal adenoma (n = 807 cases, 2,185 controls), the association of calcium with adenoma did not differ according to magnesium and phosphorus intakes, and associations of calcium:magnesium and calcium:phosphorus ratios with adenoma did not substantially

differ from those involving calcium alone (12). In the above noted French prospective cohort study (15), there was no association of a calcium:phosphorus ratio with risk for colorectal neoplasms.

In summary, calcium has been consistently associated with risk in a substantial number of studies; magnesium has been inversely associated with risk in a relatively small number of studies; the findings for iron have been unclear; and there are no data on associations of potassium or sodium with colorectal neoplasms. These findings suggest that multiple minerals, which as noted in Table 1, may plausibly affect colorectal adenoma risk. Although a combined mineral score colorectal adenoma association has not been previously reported, other similarly constructed scores to account for multiple, interacting exposures that individually may modestly affect risk are increasingly reported. For example, oxidative balance scores, comprised of anti- and pro-oxidant exposures, were inversely associated with colorectal adenoma and cancer (17,18).

Strengths and Limitations

The major strength of our study is the use of a composite mineral score to summarize the possible collective contributions of multiple mineral exposures to colorectal adenoma risk. Whereas the contributions of individual minerals to risk for colorectal adenoma may be small, collectively they may be substantial. The mineral score method allowed us to summarize overall mineral exposure while accounting for the biological interactions among the minerals. Other strengths of our study include the large sample size, accurate and complete data on colorectal adenoma cases; FFQ completion prior to colonoscopy, thus reducing reporting bias; data on many potential confounding

variables; the use of a validated dietary assessment instrument; and our multiple sensitivity analyses. Study limitations include the known limitations of food frequency questionnaires (e.g., recall error, limited number of food choices) and measuring diet only once. Different versions of the Willett FFQs were used across the 3 studies, data for intakes of magnesium, selenium and iodine were not collected in one or more of the studies, leading us to exclude those mineral intakes from our mineral score. Some of the community controls in the CPRU study could have been undiagnosed cases, had they undergone a colonoscopy or sigmoidoscopy. The endoscopy cases and controls may not have been representation of the general population, as the chances of undergoing a colonoscopy may be higher among those with symptoms, a family history of colorectal cancer, or who were highly health conscious. Additional limitations of the study are general limitations of case-control studies, such as the inability to assess temporality. The generalizability of our study was also limited, as most of our study subjects are white.

In conclusion, our findings, do not suggest that higher intakes of calcium, magnesium, zinc, and potassium combined with lower intakes of iron, copper, phosphorus, and sodium are associated with risk for colorectal adenoma.

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Table 1. Mineral score components, rationale for their inclusion, and common dietary sources

Component	Rationale for inclusion	Common dietary sources
Possibly predominately colon anti-carcinogenic		
Calcium	Binds to bile acids and free fatty acids, and mediates E-cadherin and β-catenin expression through the calcium-sensing receptors, thus modulating the APC colon carcinogenesis pathway; inducing terminal differentiation and inhibition of proliferation (5,6)	Dairy products, grains, supplements (19)
Magnesium	Prevention of mutations in colonic epithelium and maintenance of stability of the genome, oxidative stress reduction through improved insulin sensitivity; competes with calcium for intestinal absorption and transport (16,20)	Seafood, whole grains, green leafy vegetables, supplements (21)
Zinc	Essential component of the antioxidant enzyme, Cu/Zn-SOD; activates extracellular signal regulated kinases which suppresses the proliferation of colorectal cancer cells; inhibits NADPH oxidases (8,22)	Red meat, poultry, oysters, supplements (23)
Potassium	Inhibition of proliferation of many cell types including colorectal cancer cells and regulation of intracellular osmolarity through voltage gated potassium channels (24)	Legumes, potatoes, meat, nuts (25)
Possibly predominately colon pro-carcinogenic		
Iron	Damages lipid, protein, DNA and other nucleic acid by producing free radicals and catalyzing oxidative reactions; causes lipoperoxidation resulting in cell proliferation in the colonic mucosa (22)	Red meat, green leafy vegetables, grains, supplements (26)
Copper	Generation of RONS by Fenton reaction; catalyzes oxidative reactions; essential component of antioxidant enzyme, Cu/Zn-SOD; has both antioxidant and prooxidant properties (8,9,27)	Shellfish, organ meats, supplements, whole grains (28)
Phosphorus	Phosphate binds calcium and prevents calcium from binding to bile acids, thus hindering absorption of calcium; exposure of cells to high serum inorganic phosphorus concentration leads to alterations in cell function; absorbed rapidly as hormonal mechanisms maintain serum inorganic phosphate concentration within narrow limits (15,29)	Grains, milk, meat (30)

Sodium	Hampers with catabolism of cortisol (31,32); may impair colonic epithelial immune defenses; decreases activity of 11β-hydroxysteroid dehydrogenase type 2 in the colonic epithelium	Processed foods, salt (33)

Abbreviations: APC, adenomatous polyposis coli; Cu/Zn, copper-zinc; SOD, superoxide dismutase; NADPH, nicotinamide adenine dinucleotide phosphate; RONS, reactive oxygen and nitrogen species.

Table 2: Selected characteristics of participants in a pooled case-control study of incident, sporadic colorectal adenomas.[a]

	Cases (n = 779)	**Controls (n = 2,026)**	**p-value[d]**
Age (yr)	58.1 (9.2)	54.5 (10.9)	<0.0001
Male (%)	61.2	42.7	<0.0001
White (%)	94.7	96.3	0.05
Family history (%)[b]	16.9	17.9	0.47
College education or higher (%)	49.5	56	0.10
Current smokers (%)	24.3	14	<0.0001
Current drinkers (%)	67.4	57.7	<0.0001
BMI (%)			
<25 kg/m^2	33.2	40.9	0.001
25-30 kg/m^2	39.8	37.2	
>30 kg/m^2	26.7	21.8	
Waist-to-hip ratio	0.93 (0.16)	0.88 (0.15)	<0.0001
Physical activity (MET-hr/wk)	37.4 (39.4)	35.9 (34.9)	0.42
Total aspirin/NSAID use (%)[c]	35.8	41.6	0.004
Total energy intake (kcal/day)	2,075 (768)	1,987 (716)	0.01
Total fat (% total kcals)	46.6 (29)	36.3 (20.7)	<0.001
Total fruit (servings/day)	2.3 (1.8)	2.6 (1.9)	0.0002
Total vegetables (servings/day)	3.7 (2.2)	3.8 (2.4)	0.58
Total meat (servings/day)	2 (1.1)	1.7 (1)	0.0001
Red meat (servings/day)	0.7 (0.5)	0.6 (0.5)	
Processed meats (servings/day)	0.4 (0.4)	0.3 (0.3)	
Dietary fiber (g/day)	21.9 (9.6)	22.3 (10)	0.71
Mineral score[e]	15.95 (2.97)	16.01 (3.04)	0.64

Abbreviations: MET, metabolic equivalents of task; NSAID, nonsteroidal anti-inflammatory drug
[a] Values presented are mean (standard deviation) unless otherwise specified
[b] Family history of colorectal cancer in a first degree relative
[c] Regularly take aspirin or other NSAID ≥ once per week
[d] From chi square test for categorical variables and t-test for continuous variables
[e] Mineral score calculated from food and supplemental intakes of calcium, magnesium, zinc, potassium, iron, copper, phosphorus, and sodium as described in the text.

Table 3: Multivariable-adjusted associations of mineral intake scores with incident, sporadic colorectal adenomas in pooled case-control study (n = 2,805)

						Among nonregular users of aspirin and NSAIDs		
		Initial model[a]		Full model[b]			Full model[c]	
Quintiles	**No. of cases/controls (n = 779/2,026)**	**OR**	**95% CI**	**OR**	**95% CI**	**No. of cases/controls (n = 500/1,182)**	**OR**	**95% CI**
Total minerals								
1	143/358	**1.00 (ref)**		**1.00 (ref)**		89/204	**1.00 (ref)**	
2	101/228	**1.15**	0.83, 1.58	**1.16**	0.84, 1.60	59/132	**1.02**	0.68, 1.55
3	218/575	**1.01**	0.78, 1.32	**1.02**	0.78, 1.32	144/334	**1.00**	0.72, 1.39
4	102/264	**1.10**	0.80, 1.51	**1.13**	0.82, 1.55	74/149	**1.26**	0.85, 1.87
5	215/601	**1.03**	0.79, 1.34	**1.05**	0.81, 1.37	134/363	**0.96**	0.69, 1.35
P_{trend}[d]		0.27		0.57			0.85	
Dietary minerals								
1	101/264	**1.00 (ref)**		**1.00 (ref)**		66/145	**1.00 (ref)**	
2	117/266	**1.15**	0.83, 1.60	**1.13**	0.81, 1.58	75/150	**1.02**	0.67, 1.56
3	266/654	**1.25**	0.94, 1.66	**1.21**	0.90, 1.61	160/380	**1.02**	0.71, 1.47
4	118/315	**1.23**	0.89, 1.72	**1.19**	0.85, 1.67	79/189	**1.07**	0.71, 1.62
5	177/527	**1.16**	0.86, 1.58	**1.10**	0.80, 1.50	120/318	**0.98**	0.66, 1.44
P_{trend}[d]		0.27		0.37			0.75	
Supplemental minerals[e]								
1	73/281	**1.00 (ref)**		**1.00 (ref)**		40/143	**1.00 (ref)**	
2	47/176	**1.03**	0.67, 1.58	**1.09**	0.71, 1.69	26/88	**1.15**	0.64, 2.08
3	659/1,569	**1.62**	1.22, 2.16	**1.56**	1.17, 2.08	434/951	**1.62**	1.10, 2.38
P_{trend}[d]		0.15		0.35			0.95	

Abbreviations: NSAID, nonsteroidal anti-inflammatory drugs; OR, odds ratio; 95% CI, 95% confidence interval; ref, reference.

[a]Adjusted for study, age, sex, and total energy intake.

[b]Adjusted for study, age, sex, family history of colorectal adenomas in a first degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, total energy intake, total fat intake (energy adjusted).

[c]Among those who did not take aspirin or other NSAIDs adjusted for study, age, sex, family history of colorectal adenomas in a first degree relative, total energy intake, total fat intake (energy adjusted).

[d]P_{trend} calculated using sex-specific median for each quintile (for total and dietary minerals) and for each tertile (for supplementary) of mineral intake as a continuous variable.

[e]Supplementary mineral intake was categorized as three groups (none and according to the median dose for those who did take mineral supplements) due to a small sample size

Table 4: Multivariable-adjusted associations[a] of the total mineral intake score with incident, sporadic colorectal adenomas, according to selected participant chararcteristics, in pooled case-control study (n = 2,805)

	Quin-tiles	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI
Age (yr)			***<56***			***≥56***	
	1	41/200	**1.00 (ref)**		102/158	**1.00 (ref)**	
	2	39/132	**1.47**	0.87, 2.45	62/96	**1.03**	0.67, 1.57
	3	92/286	**1.64**	1.07, 2.53	126/289	**0.74**	0.53, 1.04
	4	41/135	**1.54**	0.92, 2.57	61/129	**0.91**	0.60, 1.37
	5	73/284	**1.43**	0.91, 2.24	142/317	**0.84**	0.60, 1.18
Sex			***Male***			***Female***	
	1	84/148	**1.00 (ref)**		59/210	**1.00 (ref)**	
	2	69/104	**1.32**	0.86, 2.02	32/124	**0.98**	0.60, 1.62
	3	140/247	**1.12**	0.78, 1.61	78/328	**0.90**	0.60, 1.33
	4	64/112	**1.27**	0.82, 1.95	38/152	**0.99**	0.61, 1.59
	5	120/257	**1.09**	0.76, 1.58	95/344	**1.00**	0.68, 1.47
FHCC			***Yes***			***No***	
	1	28/70	**1.00 (ref)**		115/288	**1.00 (ref)**	
	2	21/37	**1.35**	0.65, 2.80	80/191	**1.16**	0.81, 1.67
	3	33/105	**0.84**	0.45, 1.56	185/470	**1.09**	0.81, 1.47
	4	17/62	**0.83**	0.40, 1.70	85/202	**1.25**	0.87, 1.78
	5	33/89	**1.05**	0.56, 1.97	182/512	**1.07**	0.80, 1.44
Total fat (% total kcals)			***<31.8 (median)***			***≥31.8 (median)***	
	1	42/156	**1.00 (ref)**		101/202	**1.00 (ref)**	
	2	34/103	**1.22**	0.72, 2.08	67/125	**1.12**	0.75, 1.69
	3	87/315	**1.02**	0.67, 1.56	131/260	**1.00**	0.71, 1.41
	4	47/159	**1.12**	0.69, 1.82	55/105	**1.12**	0.72, 1.72
	5	113/348	**1.72**	0.78, 1.77	102/253	**0.95**	0.67, 1.36
Total Vitamin E (mg)			***<10.65 (median)***			***≥10.65 (median)***	
	1	91/176	**1.00 (ref)**		52/182	**1.00 (ref)**	
	2	49/101	**1.04**	0.66, 1.64	52/127	**1.44**	0.91, 2.30
	3	111/280	**0.87**	0.60, 1.25	107/295	**1.30**	0.88, 1.94
	4	44/121	**0.82**	0.52, 1.31	58/143	**1.68**	1.06, 2.65
	5	124/308	**0.93**	0.65, 1.33	91/293	**1.26**	0.83, 1.89

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; FHCC, family history of colorectal cancer in first-degree relative; mg, milligram.

[a]Adjusted for study, age, sex, family history of colorectal cancer in first-degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, total energy intake, total fat intake (energy-adjusted). drugs, total energy intake, total fat intake (energy adjusted).

Table 5. Multivariable-adjusted associations[a] of the total mineral score with incident, sporadic colorectal adenomas by characteristics of the largest adenoma.

	Quintiles	No. of cases/controls	OR	95% CI	No. of cases/controls	OR	95% CI
Atypia			***Mild***			***>Mild***	
	1	30/358	1.00 (ref)		99/358	1.00 (ref)	
	2	15/228	**1.37**	0.57, 3.25	76/228	**1.22**	0.86, 1.74
	3	30/575	**0.83**	0.42, 1.67	170/575	**1.08**	0.81, 1.45
	4	7/264	**0.71**	0.24, 2.07	86/264	**1.22**	0.86, 1.71
	5	15/601	**0.79**	0.35, 1.79	179/601	**1.11**	0.83, 1.49
Location			***Proximal[b]***			***Distal[c]***	
	1	35/358	1.00 (ref)		95/358	1.00 (ref)	
	2	15/228	**0.76**	0.39, 1.47	78/228	**1.37**	0.96, 1.96
	3	48/575	**0.90**	0.56, 1.45	152/575	**1.09**	0.80, 1.48
	4	25/264	**1.12**	0.64, 1.97	71/264	**1.20**	0.84, 1.74
	5	43/601	**0.90**	0.56, 1.48	153/601	**1.11**	0.82, 1.50
Shape			***Pedunculated***			***Sessile***	
	1	35/358	1.00 (ref)		88/358	1.00 (ref)	
	2	19/228	**0.96**	0.52, 1.74	65/228	**1.23**	0.84, 1.79
	3	58/575	**1.09**	0.69, 1.73	112/575	**0.87**	0.63, 1.20
	4	26/264	**1.28**	0.73, 2.23	62/264	**1.12**	0.77, 1.65
	5	57/601	**1.17**	0.74, 1.87	111/601	**0.91**	0.66, 1.26
Size			***<1 cm***			***≥1 cm***	
	1	97/358	1.00 (ref)		46/358	1.00 (ref)	
	2	68/228	**1.11**	0.77, 1.62	33/228	**1.27**	0.78, 2.09
	3	150/575	**0.99**	0.74, 1.35	68/575	**1.03**	0.68, 1.55
	4	66/264	**1.06**	0.74, 1.54	36/264	**1.28**	0.79, 2.07
	5	153/601	**1.08**	0.79, 1.47	62/601	**0.95**	0.63, 1.45
Subtype			***Tubular***			***Villous/tubulovillous***	
	1	112/358	1.00 (ref)		30/358	1.00 (ref)	
	2	64/228	**0.95**	0.66, 1.37	34/228	**1.76**	1.03, 2.99
	3	159/575	**0.96**	0.72, 1.29	51/575	**1.04**	0.64, 1.68
	4	74/264	**1.08**	0.76, 1.54	28/264	**1.26**	0.72, 2.18
	5	155/601	**1.00**	0.75, 1.35	55/601	**1.07**	0.67, 1.73

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.
[a]Adjusted for study, age, sex, family history of colorectal cancer in first-degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, total energy intake, total fat intake (energy-adjusted). drugs, total energy intake, total fat intake (energy adjusted).
[b]Cecum, ascending colon, hepatic flexure, transverse colon.
[c]Splenic flexure, descending colon, sigmoid colon, rectum.

Table 6. Multivariable-adjusted joint/combined associations[a] of anti-carcinogenic and pro-carcinogenic components of the mineral score[b] with incident colorectal adenoma

		Anti-carcinogenic mineral score tertiles		
		1 **OR (95% CI)**	**2** **OR (95% CI)**	**3** **OR (95% CI)**
Pro-carcinogenic mineral score tertiles	**1**	**1.00 (ref)**[c]	**0.59** (0.18, 1.87)	**0.57** (0.19, 1.74)
	2	**0.50** (0.16, 1.60)	**0.51** (0.17, 1.56)	**0.49** (0.16, 1.51)
	3	**0.72** (0.24, 2.19)	**0.65** (0.21, 1.99)	**0.63** (0.19, 2.11)

Abbreviations: CI, confidence interval; HR, hazards ratio; Ref, referent.

[a]From multivariable logistic regression; adjusted for study, age, sex, family history of colorectal cancer in first-degree relative, regular use of aspirin or nonsteroidal inflammatory drugs, total energy intake, total fat intake (energy-adjusted).

[b]Mineral scores calculated from food and supplemental intakes of calcium, copper, iron, magnesium, phosphorus, potassium, sodium, and zinc as described in the text; anti-carcinogenic components included calcium, magnesium, potassium, and zinc; pro-carcinogenic components included copper, iron, phosphorus, and sodium.

[c]Reference category: low anti-carcinogenic/high pro-carcinogenic mineral intakes (least anti-carcinogenic mineral intake ranked as 1 /highest pro-carcinogenic mineral intake ranked as 1).

Supplement Table 1. Multivariable-adjusted joint/combined associations[a] of dietary mineral intake and supplementary mineral intake components of the mineral score[b] with incident colorectal adenoma

		Dietary mineral intake score tertiles		
		3 **OR (95% CI)**	**2** **OR (95% CI)**	**1** **OR (95% CI)**
Supplementary mineral intake score tertiles	**1**	**1.00 (ref)**[c]	**0.78** (0.33, 1.80)	**0.44** (0.15, 1.33)
	2	**1.36** (0.49, 3.80)	**0.76** (0.31, 1.88)	**0.93** (0.34, 2.50)
	3	**1.28** (0.65, 2.51)	**1.49** (0.76, 2.95)	**1.25** (0.63, 2.48)

Abbreviations: CI, confidence interval; HR, hazards ratio; Ref, referent.

[a]From multivariable logistic regression; adjusted for study, age, sex, family history of colorectal cancer in first-degree relative, regular use of aspirin or nonsteroidal inflammatory drugs, total energy intake, total fat intake (energy-adjusted).

[b]Mineral scores calculated from food and supplemental intakes of calcium, iron, and zinc as described in the text; anti-carcinogenic components included calcium and zinc; pro-carcinogenic components included iron.

[c]Reference category: high dietary/low supplemental mineral intakes.

Supplement Table 2. Sensitivity analyses for mineral score components: associations[a] of the mineral score[b] with risk for incident colorectal adenoma, with removal/replacement of each score component one at a time

Mineral removed	Mineral score continuous	Mineral score upper quintile
	OR (95% CI)	OR (95% CI)
Calcium	**1.02** (0.98, 1.05)	**1.13** (0.87, 1.47)
Magnesium	**1.02** (0.98, 1.05)	**1.18** (0.92, 1.53)
Zinc	**1.01** (0.98, 1.04)	**1.07** (0.83, 1.38)
Potassium	**1.02** (0.99, 1.06)	**1.16** (0.88, 1.52)
Iron	**0.98** (0.95, 1.01)	**0.84** (0.63, 1.11)
Copper	**0.98** (0.95, 1.01)	**0.87** (0.66, 1.15)
Phosphorus	**0.99** (0.97, 1.02)	**1.10** (0.82, 1.49)
Sodium	**1.02** (0.99, 1.06)	**1.31** (0.99, 1.74)

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]From multivariable logistic regression; adjusted for study, age, sex, family history of colorectal cancer in first-degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, total energy intake, total fat intake (energy-adjusted).

[b]Mineral score calculated from food and supplemental intakes of calcium, magnesium, zinc, potassium, iron, copper, phosphorus, and sodium as described in the text.

Supplement Table 3. Sensitivity analyses for mineral score components: associations[a] of each mineral score[b] component with risk for incident colorectal adenoma, adjusted for the remaining 7-component score

Individual mineral score components	Associations for upper relative to lowest quintile
	OR (95% CI)
Calcium	**0.98** (0.72, 1.33)
Magnesium	**0.96** (0.64, 1.43)
Potassium	**0.89** (0.65, 1.25)
Zinc	**1.04** (0.76, 1.44)
Copper	**0.68** (0.49, 0.94)
Iron	**0.65** (0.48, 0.91)
Phosphorus	**1.04** (0.73, 1.50)
Sodium	**1.50** (1.21, 2.01)

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]From multivariable logistic regression; adjusted for study, age, sex, family history of colorectal cancer in first-degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, total energy intake, total fat intake (energy-adjusted).

[b]Mineral score calculated from food and supplemental intakes of calcium, magnesium, zinc, potassium, iron, copper, phosphorus, and sodium as described in the text.

Supplement Table 4. Correlation among components of the mineral score in the pooled case-control studies of incident, sporadic colorectal adenoma (n = 2,805)

	Pearson correlation coefficients							
	Ca	**Mg**	**K**	**Zn**	**Cu**	**Fe**	**P**	**Na**
Calcium (Ca)	1.00							
Magnesium (Mg)	0.58	1.00						
Potassium (K)	0.59	0.86	1.00					
Zinc (Zn)	0.26	0.42	0.30	1.00				
Copper (Cu)	0.36	0.74	0.59	0.48	1.00			
Iron (Fe)	0.25	0.40	0.29	0.36	0.45	1.00		
Phosphorus (P)	0.69	0.83	0.85	0.36	0.55	0.31	1.00	
Sodium (Na)	0.48	0.68	0.75	0.27	0.49	0.26	0.79	1.00