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# Combined Mineral Intakes and Risk of Colorectal Cancer in Postmenopausal Women

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## Abstract

**Background:** Despite considerable biological plausibility, other than for calcium, there are few reported epidemiologic studies on mineral intake-colorectal cancer (CRC) associations, none of which investigated multiple minerals in aggregate.

**Methods:** Accordingly, we incorporated 11 minerals into a mineral score and investigated its association with incident CRC in the Iowa Women's Health Study, a prospective cohort study of 55 – 69-year-old women who completed a food frequency questionnaire in 1986. In the analytic cohort (n = 35, 221), 1,731 incident CRC cases were identified via the State Health Registry of Iowa. Participants' calcium, magnesium, manganese, zinc, selenium, potassium, and iodine intakes were ranked 1 – 5, with higher ranks indicating higher, potentially anti-carcinogenic, intakes, whereas for iron, copper, phosphorus, and sodium intakes, the rankings were reversed to account for their possible pro-carcinogenic properties. The rankings were summed to create each woman's mineral score. The mineral score-incident CRC association was estimated using multivariable Cox proportional hazards regression.

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Disclosure of Potential Conflicts of Interest

None of the authors has a conflict of interest to disclose.

Disclaimer

The findings and conclusions contained within are those of the authors and do not necessarily reflect positions or policies of the National Cancer Institute. The National Cancer Institute had no influence on the analysis and interpretation of the data, the decision to submit the manuscript for publication, or the writing of the manuscript.

**Results:** There was decreasing risk with an increasing score (*P*-trend = 0.001). The hazard ratios and 95% confidence intervals (CI) for those in mineral score quintiles 2 – 5 relative to those in the lowest were 0.91 (CI, 0.88–1.08), 0.85 (CI, 0.75–0.95), 0.86 (CI, 0.75–0.97), and 0.75 (CI, 0.71–0.95), respectively.

**Conclusions:** Our findings suggest that a predominance of putative anti- relative to pro-colorectal carcinogenic mineral intakes may be inversely associated with CRC risk.

**Impact:** These results support further investigation of CRC etiology using composite mineral intake scores.

### Keywords

Colorectal Cancer; Mineral Scores; Iowa Women's Health Study; Dietary Patterns

## Introduction

Colorectal cancer (CRC) is the second most common cause of cancer-related deaths in the U.S. (1). Findings from epidemiologic studies indicate that environmental factors—especially diet and lifestyle—play an important role in CRC risk (2,3). As summarized in Table 1, there is considerable biological plausibility for minerals (including calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus, and sodium) affecting risk of colorectal carcinogenesis. Calcium has been consistently modestly inversely associated with colorectal neoplasms in multiple observational studies (4,5,33). However, relatively few studies reported associations of other mineral intakes with CRC, and the limited results are less consistent.

There are several possible reasons for the inconclusive epidemiologic results for minerals other than calcium, including biologic interactions among minerals and that the contributions of individual minerals to CRC risk may be small. Examples of biologic interactions include that calcium competes with magnesium for intestinal absorption and transport (7), and similar interactions were found between copper and iron (24), and copper and zinc (13). Hephaestus, a protein found in the colon, is a copper-dependent ferroxidase responsible for dietary iron transport (24). Balanced levels of copper and zinc are thought to contribute to proper functioning of copper-zinc superoxide dismutase, an anti-oxidation enzyme with tumor suppressive properties (13). Although the contributions of individual minerals to risk may be small, it is possible that collectively they may be substantial. A method increasingly used to account for the possible combined effects of multiple, often correlated, interacting exposures is dietary scores (34).

Relatively few reported studies investigated associations of specific minerals, other than calcium, with CRC risk, and to our knowledge, none considered the possible aggregate effects of multiple minerals. Accordingly, we investigated associations of calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus, and sodium intakes combined into a mineral intake score, with CRC incidence in a prospective cohort study.

## Materials and Methods

### Study population

The Iowa Women's Health Study, established in 1986, is a prospective cohort study of post-menopausal Iowa women (35,36). Prospective participants were 55 – 69-year-old women on the Iowa Department of Transportation 1985 current drivers list, from whom 50% were randomly selected. Of these, 99,826 had a valid Iowa mailing address and were mailed a questionnaire, of whom 41,836 (42.7%) responded and were eligible for enrollment. Respondents, relative to non-respondents, were, on average, 3 months older and had a slightly lower body mass index (BMI), income, and education, and were more likely to reside in more rural counties (35). Cancer incidence did not substantially differ between respondents and non-respondents.

The baseline questionnaire included questions on demographics, diet, family history, medical and reproductive history, smoking, physical activity, and body size characteristics. Written instructions and tape measures were provided so that the participant could have someone measure their waist circumference (1 inch above the umbilicus) and hip circumference (maximal protrusion) for waist-hip ratio calculations. BMI was calculated as self-reported weight over self-reported height squared ($kg/m^2$). The dietary portion of the questionnaire was a Willett 127-item semi-quantitative food frequency questionnaire (FFQ). Participants reported their usual food consumption over the previous year, referencing a commonly used serving size, according to nine frequency categories ranging from never or < 1 serving/month to ≥ 6 servings/day. The questionnaire also solicited intakes of multivitamin/mineral and specific vitamin and mineral supplements. Total energy and nutrient intakes were calculated by adding energy and nutrients from all food sources using the dietary database developed by Willett, *et al* (37). In addition to the original survey, follow-up surveys were sent to study participants in 1987, 1989, 1992, 1997, and 2004. Aspirin and other nonsteroidal anti-inflammatory drug use was not collected until 1992, and diet was only comprehensively reassessed in 2004 at which time only 68.3% of the participants remained alive.

Deaths were identified through the State Health Registry of Iowa and the National Death Index. Cancer diagnoses were collected through linkage with the State Health Registry of Iowa, a participant in the National Cancer Institute's Surveillance, Epidemiology, and End Results Program; ascertainment of cancer diagnoses was nearly 100% (35,36). CRC was defined as adenocarcinoma of the colon or rectum (ICD-O-3 codes: C18.0–18.9, C19.9, and C20.9). Follow-up time was calculated as the time between the date of completing the baseline questionnaire and age at first CRC diagnosis, date when they moved from Iowa, or date of death; if none of these events occurred, the subject was assumed to be alive, cancer-free, and living in Iowa, and censored at the end of follow up (December 31, 2012) (35,36).

### Analytic cohort and incident CRC

Women who reported a history of cancer other than non-melanoma skin cancer at baseline (n = 3,830), left ≥ 30 FFQ items blank (n = 2,499), or reported implausible total daily energy intakes (< 600 or > 5,000 kcal/day) (n = 286) were excluded from the analytic cohort,

leaving 35,221 participants, including 1,731 who developed CRC during follow up, for analysis.

### Mineral score components and their assessment

The FFQ-derived food and supplement data were used to calculate mineral scores for all participants. The 11 components in the mineral score, the rationale behind their inclusion, and their predominant sources are listed in Table 1. For most mineral intakes, we summed values derived from foods and supplements. Measurements of dietary selenium and iodine are unreliable because their intakes depend on their abundance in soil, which varies substantially around the world (38,39). Therefore, only supplemental selenium and iodine intakes were used. 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 analytic cohort at baseline. For each mineral hypothesized to reduce CRC risk, each participant 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 woman's values for each mineral were summed to represent her mineral score; thus, the range of possible scores was 11 – 55.

### 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 (CI) that excluded 1.0 was considered statistically significant. Selected participant characteristics at baseline across quintiles of the mineral score were summarized and compared using $\chi^2$ tests for categorical variables and analysis of variance for continuous variables (the latter transformed by the natural logarithm when needed to improve normality). The association of the mineral score—as a continuous variable and categorized according to quintiles—with risk of incident CRC was estimated using multivariable Cox proportional hazards regression to calculate hazard ratios (HR) and their 95% CIs. The covariates, chosen *a priori* as previously having been found to be strong risk factors for CRC, included age, total energy intake, height, BMI, waist-hip ratio, smoking, physical activity, hormone replacement therapy (HRT) use, education, family history of CRC in a first degree relative, and diabetes; total fat, dietary fiber, total fruits and vegetables, total red and processed meats, and alcohol intakes; and a dietary oxidative balance score (OBS). An equal-weight dietary OBS, as described by Dash et al., included the dietary antioxidants α-carotene, β-carotene, β-crypotoxanthin, lutein, lycopene, vitamin C, vitamin E, omega-3 fatty acids, and flavonoids, and the dietary pro-oxidants omega-6 fatty acids and saturated fat (40,41). A test for trend was calculated using the median value for each quintile of the mineral score.

The above models were also applied in stratified analyses, which were conducted to examine the association of the mineral score with CRC incidence according to categories of selected covariates. Strata for the following continuous variables were created based on values above

and below the population median: age, height, waist-hip ratio, dietary OBS, and total energy, total fat, dietary fiber, total fruits and vegetables, and total red and processed meats intakes. Strata for other variables were as follows: smoking—current, former, never; alcohol intake—none, > 0 g – < 15 g/day, ≥ 15 g/day; physical activity—tertiles; HRT use—current, former, never; BMI (according to WHO criteria)—< 25, 25 – 30, ≥ 30 kg/m$^2$; family history of CRC in a first degree relative—yes/no; personal history of diabetes—yes/no; and education—≥ college graduate/< college graduate. Effect-measure modification was assessed by comparing stratum-specific hazard ratios.

The analyses were also repeated separately for different CRC sites. Incident CRC in the cecum, appendix, ascending colon, hepatic flexure, transverse colon, and overlapping colon lesions (ICD-O-3 codes C18.0 – 18.4, C18.8 – 18.9) were categorized as proximal CRC (n = 971, 56% of total cases), and cancers in the splenic flexure, descending colon, sigmoid colon, rectosigmoid junction, and rectum (ICD-O-3 codes C18.5 – C18.7, C19.9, C20.9) were categorized as distal CRC (n = 760, 44% of total cases). No cases had missing codes or unspecified sub-sites.

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. First, we investigated whether including in our models one or more variables to represent supplement-taking behaviors (multivitamin and/or other supplement use) materially affected our estimated associations. Second, we created separate supplement-only and diet-only mineral scores, categorized each of the two scores into five categories based on their distributions, and assessed their joint/combined association with CRC. For the latter analysis, the reference category was participants who jointly took no supplemental minerals and had a low diet-only mineral score. Third, similarly as for the latter analysis, we created separate anti- and pro-carcinogenic mineral scores, assessed their correlation with Pearson correlation coefficients, and then categorized the two scores into quintiles and assessed their joint/combined association with CRC. For the latter analysis, the reference category was participants who had a joint low anti-carcinogenic mineral score/high pro-carcinogenic mineral score. A $P_{\text{interaction}}$ was calculated in a multivariable model in which both scores were entered as continuous variables, along with a anti-carcinogenic mineral score*pro-carcinogenic mineral score interaction term; the *P*-value for the multiplicative interaction term was taken as the $P_{\text{interaction}}$. Fourth, we took individual mineral components in and out of the mineral score one at a time and assessed the associations of a) the remaining 10-component scores with CRC, and b) each mineral score component individually with CRC, adjusted for its respective remaining 10-component mineral score.

In additional sensitivity analyses, we assessed whether adjustment for aspirin and other nonsteroidal anti-inflammatory drug use affected the mineral score-CRC association by including only subjects who replied to the 1992 follow-up questionnaire regarding the use of aspirin and other nonsteroidal anti-inflammatory drugs. To reduce ambiguity in the temporal relation between the mineral score and incident CRC, we excluded participants who were

diagnosed with CRC or died during the first year of follow up. We also assessed censoring participants when they reached the age of 75.

## Results

Selected characteristics of the participants at baseline by quintiles of the mineral score are summarized in Table 2. Study participants were, on average, 61 years of age, and 99% were white. Those in the higher mineral score quintiles tended to be less educated and more likely to have diabetes, a normal BMI, and a higher physical activity level than those in the lower quintiles. On average, participants in the upper relative to the lower quintiles had a smaller waist-hip ratio; higher total fat, dietary fiber, and total fruits and vegetables intakes; and lower total energy and red and processed meats intakes.

The associations of the mineral score with risk of incident CRC estimated using Cox proportional hazards regression models are summarized in Table 3. Adjustment for multiple known and suspected risk factors had a minimal effect on the risk estimates. In the multivariable-adjusted analyses, for each one-point increase in the mineral score, there was an estimated statistically significant 2% lower risk for incident CRC. When analyzed by quintiles, there was a statistically significant trend for decreasing CRC risk with an increasing score, and those in the upper relative to the lowest quintile were at a statistically significant approximately 25% lower risk. There were no substantial or consistent differences in our findings in relation to colon site (Supplement Table 1) or according to levels of the other risk factors noted in the statistical section (Supplement Table 2).

The results of the sensitivity analyses were as follows. Adjustment for multivitamin and/or other supplement use did not materially alter our results (Supplement Table 3). In the joint/combined analysis of the diet-only and supplement-only mineral scores (Table 4), there was 1) decreasing risk with an increasing diet-only mineral score among those who did not take supplemental minerals, culminating in an HR of 0.84 (95% CI 0.80–0.88) among those in the upper diet-only mineral score quantile; 2) decreasing risk with an increasing supplement-only mineral score among those in the lowest diet-only mineral score quantile, culminating in an HR of 0.87 (0.82– 0.90) among those in the upper supplement-only mineral score quantile; and 3) the lowest risk (HR, 0.66; 95% CI 0.63–0.68) was found among those who were in the joint high diet-only/high supplement-only mineral score category relative to those who were in the joint low diet-only/no supplemental minerals category.

In other sensitivity analyses, the correlation between the anti- and pro-carcinogenic mineral scores was r = 0.23 ($P = 0.06$). In the joint/combined analysis of the anti- and pro-carcinogenic mineral scores (Supplement Table 4), the lowest risk (HR, 0.69; 95% CI 0.61–0.87) was found among those who were in the joint high anti-carcinogenic/low pro-carcinogenic mineral score category relative to those who were in the joint low anti-carcinogenic/high pro-carcinogenic mineral score category ($P_{interaction} = 0.04$). The risk estimates after removal and replacement of each score component one at a time (Supplement Table 5) differed only minimally from those with the full score. The associations of each individual score mineral—adjusted for its respective remaining 10-component mineral score—with CRC were all less than that for the overall mineral score (Supplement Table 6). For

those in the upper relative to the lowest intake quintiles of the putative anti-carcinogenic minerals, the estimated HRs ranged from 0.84 for total calcium intake to 0.99 for total zinc intake, and for the putative pro-carcinogenic minerals they ranged from 1.01 for sodium to 1.21 for copper.

Finally, in additional sensitivity analyses, exclusion of those who died or were diagnosed with CRC during their first year of follow up, or censoring participants when they reached age 75 had negligible impact on the risk estimates (Supplement Table 7). When we used 1992 as the baseline for follow-up, additional adjustment for aspirin and other NSAID use did not materially alter the results (Supplement Table 8).

## Discussion

Our findings suggest that higher calcium, magnesium, manganese, zinc, selenium, potassium, and iodine intakes, combined with lower iron, copper, phosphorus, and sodium intakes may be associated with lower risk of incident CRC. As discussed below, our findings are consistent with much of the data available from previous studies on associations of calcium, magnesium, zinc, selenium, iodine, iron, copper, and phosphorus intakes individually with CRC risk. Our findings of decreasing risk of CRC with an increasing mineral score supports the antioxidant-related and other anti-colon carcinogenic effects of calcium, magnesium, manganese, zinc, selenium, potassium, and iodine, and the pro-oxidant and other pro-colon carcinogenic effects of iron, copper, phosphorus, and sodium. To our knowledge, there are no previous reports of associations of combined intakes of the aforementioned 11 minerals with CRC incidence.

Whereas study of calcium in relation to colorectal carcinogenesis has been considerable, study of other minerals in relation to the disease has been relatively limited. In a 2015 meta-analysis of 20 prospective cohort studies of a calcium-CRC association, the summary relative risk (RR) for those in the highest relative to those in the lowest calcium intake categories was 0.80 (95% CI, 0.70–0.92) (33). In a 2016 meta-analysis of 4 randomized, controlled trials of the efficacy of supplemental calcium on reducing colorectal adenoma recurrence, the summary RR was 0.89 (95% CI, 0.82–0.96) (42). In a 2014 meta-analysis of 4 prospective cohort studies of a magnesium-CRC association, the summary RR among those in the highest relative to the lowest category of magnesium intake was 0.78 (95% CI, 0.66–0.92) (8). In a 2013 meta-analysis of 6 prospective cohort studies of a zinc-CRC association, the summary RR for those in the highest relative to the lowest category of zinc was 0.83 (95% CI, 0.72–0.94) (43). In a 2016 meta-analysis of 10 cohort studies of associations of selenium exposure (measured as supplemental intake or serum or toenail concentrations) with CRC, the summary odds ratio (OR) for those in the highest relative to the lowest category of selenium exposure was 0.89 (95% CI, 0.67–1.17) (16). In a 2016 meta-analysis of 8 case-control and 2 prospective cohort studies of an iron-colorectal adenoma association, the summary 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) (44). In a French-based case-control study (n = 171 cases, 309 controls), which to our knowledge is the only reported

study of a copper-CRC association, the OR for those in the fourth relative to the first quartile of dietary copper intake was 2.4 (95% CI, 1.3–4.6) (25). In a French-based prospective study (n = 67,312, of whom 172 developed colorectal adenoma 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) (27). To the best of our knowledge, there are no reported studies on associations of manganese, potassium, iodine, or sodium intakes with colorectal neoplasms.

In summary, calcium has been consistently, modestly associated with risk in a substantial number of studies; magnesium, zinc, and selenium have been modestly inversely associated with risk in a relatively small number of studies; copper was directly associated with risk in the one study to investigate it; the findings for iron have been unclear; and there are no data on associations of manganese, potassium, iodine, or sodium with colorectal neoplasms. Overall, these findings suggest that multiple minerals, which as noted in Table 1 may plausibly affect CRC risk, individually may be modestly associated with CRC risk in the hypothesized directions.

A few studies investigated associations of limited combinations of certain minerals with colorectal neoplasms. In a randomized, controlled trial of calcium supplementation (1,200 mg/day) over 4 years, the RRs for adenoma recurrence among those with dietary calcium:magnesium intake ratios above and below the median at baseline were 0.98 (95% CI, 0.75–1.28) and 0.68 (95% CI, 0.52–0.90), respectively (9). 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 (7). On the other hand, in a pooled case-control study of colorectal adenoma (n = 807 cases, 2,185 controls), associations 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 (45). In the above-noted French prospective cohort study (27), there was no association of a calcium:phosphorus ratio with risk for colorectal neoplasms. In the Iowa Women’s Health Study cohort (n = 34,708), heme iron was directly associated with colon cancer incidence within each category of zinc; however, zinc was inversely associated with colon cancer incidence within each category of heme iron (14).

Although a combined mineral score has not been previously reported, other similarly constructed scores to account for multiple, interacting exposures that individually may modestly affect risk are increasingly reported. Oxidative balance scores, comprised of anti- and pro-oxidant exposures, were inversely associated with colorectal adenoma and cancer (40,41). A dietary inflammatory index, a score composed of multiple putative dietary pro- and anti-inflammatory exposures such that a higher score represents a more pro-inflammatory diet, was directly associated with CRC, other cancers, and other chronic diseases (46). In order to incorporate the synergistic effects of food items in the Mediterranean diet, the Mediterranean diet score was used to investigate associations of a Mediterranean diet pattern with CRC and cardiovascular disease, finding that higher Mediterranean diet scores are associated with lower CRC risk (47,48). The Healthy Eating

Index, a score based on recommendations from MyPyramid and the US Dietary Guidelines for Americans, was statistically significantly inversely associated with CRC risk (49).

A strength of our study is the novel composite mineral score used to summarize multiple mineral exposures. Whereas the contributions of individual minerals to risk for CRC may be small, collectively they may be substantial. Inconsistent results for individual minerals in prior epidemiologic studies may have been because the minerals individually are only weakly associated with risk, the weak associations are difficult to detect using current dietary assessment methods, and investigating individual minerals adjusted for all others does not account for the interactions (including synergisms and antagonisms) among them. Synergisms often occur on a metabolic level. For example, an adequate copper intake is necessary for iron metabolism. Antagonisms, on the other hand, usually occur on the absorption level. A high intake of calcium, for example, may suppress zinc absorption in the gastrointestinal tract. Calcium, an antagonist of magnesium, also competes with magnesium for intestinal absorption and transport. Also, in animal studies, calcium inhibited heme-induced cytotoxicity and prevented heme-induced colonic epithelial hyperproliferation (50). 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; the prospective design; accurate and complete data on CRC diagnosis; data on many potential confounding variables; the use of cancer incidence, rather than mortality, as the endpoint of interest; 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. Another limitation was the possible overestimation of fruit and vegetable intake (the reported average consumption of total fruits and vegetables in this cohort was 37.8 servings/week, or 5.4 servings/day). Also, the study population comprised only white women; thus, generalization to men, other populations, or races may be limited. Also, data on CRC screening were not collected until near the end of follow-up, after only 68.3% of the study participants remained alive; however, not being able to include CRC screening, a potential effect modifying factor, in our analyses likely attenuated our estimated associations. This is because no matter how high risk someone’s diet or lifestyle may be, if via CRC screening (which is actually mostly colorectal adenoma detection and subsequent removal) they have their adenomas removed, they are unlikely to get CRC. So, in a sense, these patients are ‘misclassified’, thus attenuating what the associations may have been had there been no screening. Finally, we cannot rule out the possibility that some supplements were taken in response to symptoms or clinical disease; however, in our sensitivity analyses, exclusion of participants who were diagnosed with CRC or died during the first year of follow up did not materially affect our estimated associations.

In conclusion, our findings, taken in context with those from previous studies, suggest that higher calcium, magnesium, manganese, zinc, selenium, potassium, and iodine intakes, combined with lower iron, copper, phosphorus, and sodium intakes may be associated with lower risk of CRC.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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; modulation of the APC colon carcinogenesis pathway through mediating E-cadherin and β-catenin expression via the calcium-sensing receptors; inhibition of proliferation and inducing terminal differentiation (4,5) | Dairy products, grains, supplements (6) |
| Magnesium | Reduces oxidative stress by improving insulin sensitivity, maintaining genome stability, and preventing mutations in colonic epithelial cells; competes with calcium for intestinal absorption and transport (7–9) | Seafood, whole grains, green leafy vegetables, supplements (10) |
| Manganese | Essential component of manganese SOD, an antioxidant enzyme that protects mitochondria from oxygen radical damage (11) | Whole grains, leafy vegetables, supplements (12) |
| Zinc | Inhibits NADPH oxidases and suppresses the proliferation of colorectal cancer cells through activation of extracellular signal regulated kinases; essential component of the antioxidant enzyme, Cu/Zn-SOD (13,14) | Red meat, poultry, oysters, supplements (15) |
| Selenium | Decreases RONS induced by androgens, ageing, or microbial gut flora; essential component of glutathione peroxidase, an antioxidant enzyme that catalyzes the breakdown of hydrogen peroxide to water, and organic hydroxyperoxides to alcohol (16) | Supplements, seafood, organ meats (17) |
| Potassium | Voltage-gated potassium channels inhibit proliferation in many cell types; voltage-gated channel conductance activates T-lymphocytes; central regulators for cell volume by governing potassium ion flow and intracellular osmolarity that drives obligatory water flow across cell membrane (18,19) | Legumes, potatoes, meat, nuts (20) |
| Iodine | Acts as an electron donor and reduces free radicals; indirectly renders amino acids, such as tyrosine and histidine, and fatty acids, such as arachadonic acid, less oxidized through iodination (21) | Supplements, dairy products, eggs, table salt additive (22) |
| Possibly predominately colon pro-carcinogenic | | |
| Iron | Primarily available from red meat; preferentially catalyzes oxidative reactions through production of free radicals, resulting in lipid, protein, and DNA and other nucleic acid damage; increases cell proliferation in the mucosa through lipoperoxidation and/or cytotoxicity of fecal water (14) | Red meat, grains, supplements (23) |
| Copper | Antioxidant and pro-oxidant properties; binds to proteins; involved in structural and catalytic properties of enzymes in oxidation processes; generates RONS by Fenton reaction; chronic copper overload leads to oxidative stress conditions; essential component of the antioxidant enzyme, Cu/Zn-SOD (13,24,25) | Shellfish, organ meats, whole grains, supplements (26) |
| Phosphorus | Rapidly absorbed as hormonal mechanisms attempt to maintain the serum inorganic phosphate concentration within narrow limits; exposure of cells to a brief high-serum inorganic phosphorus concentration potentially signals alterations in cell functions that lead to deleterious effects; phosphate binds calcium, thus preventing calcium from binding to bile acids (27,28) | Grains, meat, milk (29) |
| Sodium | Decreases 11β-hydroxysteroid dehydrogenase type 2 activity in the colonic epithelium, slowing down cortisol catabolism (19,30,31); may impair immune defenses in the colon epithelium | Processed foods, salt added to foods (32) |

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 participant characteristics at baseline across quintiles of the mineral score[a]; Iowa Women's Health Study, 1986–2012

| Characteristics[b] | Mineral score quintiles | | | | |
|---|---|---|---|---|---|
| | 1 (< 15) median = 12 (N = 5,369) | 2 (15 – 16) median = 15 (N = 6,464) | 3 (17 – 18) median = 17 (N = 7,637) | 4 (19 – 20) median = 18 (N = 7,287) | 5 (21 – 30) median = 21 (N = 8,464) |
| Age (years) | 61.7 (4.3) | 61.5 (4.1) | 61.5 (4.2) | 61.5 (4.2) | 61.5 (4.2) |
| Education < college graduate (%) | 13.5 | 16.3 | 18.8 | 18.9 | 19.7 |
| Family history of colorectal cancer[c] (%) | 2.5 | 3.3 | 3.0 | 3.4 | 3.1 |
| Diabetes at baseline (%) | 0.8 | 1.1 | 1.2 | 1.3 | 1.5 |
| Hormone replacement therapy (%) | | | | | |
| Never | 67.8 | 64.6 | 61.3 | 59.6 | 56.1 |
| Former | 8.5 | 9.7 | 11.1 | 12.1 | 14.3 |
| Current | 23.7 | 25.7 | 27.6 | 28.3 | 29.7 |
| Height (cm) | 159.9 (6.4) | 160.1 (6.2) | 160.2 (6.2) | 160.5 (6.2) | 160.7 (6.19) |
| Body mass index category (%) | | | | | |
| < 25 kg/m$^2$ | 36.9 | 39.5 | 41.4 | 42.7 | 48 |
| 25 – 30 kg/m$^2$ | 37.5 | 36.8 | 36.9 | 37.8 | 36.3 |
| ≥ 30 kg/m$^2$ | 25.6 | 23.6 | 21.7 | 19.5 | 15.7 |
| Waist-hip ratio | 0.852 (0.092) | 0.844 (0.084) | 0.841 (0.081) | 0.834 (0.082) | 0.833 (0.093) |
| Physical activity (%) | | | | | |
| Low | 57.5 | 54.9 | 48.9 | 43.7 | 37.7 |
| Medium | 25.3 | 26.1 | 27.7 | 28.4 | 29.0 |
| High | 17.3 | 19.0 | 23.4 | 27.9 | 33.4 |
| Smoking status (%) | | | | | |
| Never | 68.2 | 63.1 | 67.0 | 65.1 | 61.8 |
| Former | 15.4 | 16.5 | 18.0 | 20.8 | 24.4 |
| Current | 16.4 | 16.2 | 15.1 | 14.1 | 13.8 |
| Alcohol intake (%) | | | | | |
| None | 59.6 | 56.3 | 54.7 | 54.5 | 51.8 |
| > 0 – < 15 g/day | 34.2 | 36.3 | 38.6 | 39.5 | 41.9 |
| ≥ 15 g/day | 6.2 | 7.4 | 6.7 | 6.0 | 6.4 |
| Total energy intake (kcal/day) | 2,093 (938) | 1,968 (735) | 1,859 (697) | 1,728 (650) | 1,546 (503) |
| Total fat intake (% kcal/day) | 50.6 (19.2) | 59.1 (21.3) | 65.3 (23.1) | 74.5 (27.5) | 86.0 (43.2) |
| Dietary fiber intake (g/1,000 kcal/day) | 5.0 (2.6) | 5.1 (2.5) | 5.5 (2.8) | 5.7 (3.4) | 5.6 (2.6) |
| Take multivitamin (%) | 9.3 (8.3) | 11.4 (9.9) | 35.6 (14.2) | 41.3 (12.5) | 52.4 (17.3) |
| Take calcium supplement (%) | 30.3 (25.1) | 36.2 (23.7) | 37.9 (27.2) | 35.4 (12.9) | 34.3 (10.7) |
| Total fruits & vegetables intake (servings/wk.) | 39.1 (22.3) | 41.1 (21.1) | 44.8 (25.7) | 47.7 (32.5) | 47.5 (24. 6) |

| Characteristics[b] | Mineral score quintiles | | | | |
|---|---|---|---|---|---|
| | 1 (< 15) median = 12 (N = 5,369) | 2 (15 – 16) median = 15 (N = 6,464) | 3 (17 – 18) median = 17 (N = 7,637) | 4 (19 – 20) median = 18 (N = 7,287) | 5 (21 – 30) median = 21 (N = 8,464) |
| Total red & processed meats intake (servings/wk.) | 8.7 (7.2) | 8.1 (5.3) | 7.1 (5.0) | 6.0 (4.1) | 4.8 (3.1) |
| Dietary OBS[d] | −0.78 (0.20) | −0.73 (0.11) | −0.69 (0.13) | −0.67 (0.22) | −0.58 (0.11) |

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

[b]All variables measured at baseline (1986) and are presented as mean (SD) except as otherwise specified.

[c]In a first degree relative.

[d]Oxidative balance score; a composite of 11 anti- and pro-oxidant dietary exposures (see text); a higher score represents higher anti-oxidant relative to pro-oxidant dietary exposures; study population range: −0.97 to −0.48.

**Table 3.**

Associations[a] of the mineral score[b] with risk for incident colorectal cancer among older women (n = 35,221); Iowa Women's Health Study, 1986–2012

| | | Age- and total energy-adjusted associations | | Multivariable-adjusted associations[c] | |
|---|---|---|---|---|---|
| | # cases | HR | 95% CI | HR | 95% CI |
| **Mineral score continuous** | 1,731 | 1.00 | 0.96–1.02 | 0.98 | 0.97–1.01 |
| **Mineral score quintiles (median)** | | | | | |
| 1 (12) | 305 | 1.00 (ref) | | 1.00 (ref) | |
| 2 (15) | 350 | 0.97 | 0.85–1.10 | 0.91 | 0.88–1.08 |
| 3 (17) | 358 | 0.85 | 0.70–0.96 | 0.85 | 0.75–0.95 |
| 4 (18) | 338 | 0.87 | 0.75–1.04 | 0.86 | 0.75–0.97 |
| 5 (21) | 380 | 0.77 | 0.70–0.95 | 0.75 | 0.71–0.95 |
| *P-trend* | | *0.001* | | *0.001* | |

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

[a] From Cox proportional hazards regression.

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

[c] Adjusted for age, height, body mass index, waist-hip ratio, smoking, physical activity, hormone replacement therapy use, education, family history, diabetes, total energy intake, total fat intake, dietary fiber intake, total fruits and vegetables intake, total red and processed meats intake, alcohol, and dietary oxidative balance score (see text).

**Table 4.**

Multivariable-adjusted joint/combined associations[a] of supplement-only and diet-only mineral scores[b] with incident colorectal cancer in the Iowa Women's Health Study (n = 35,221), 1986 – 2012

| | | Supplement-only mineral score quantiles[c] | | | | |
|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 |
| | | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| Diet-only mineral score quantiles[d] | 1 | 1.00 (Ref)[e] | 0.94 (0.92–0.99) | 0.92 (0.89–0.93) | 0.89 (0.84–0.92) | 0.87 (0.82–0.90) |
| | 2 | 0.91 (0.90–1.00) | 0.91 (0.84–0.88) | 0.86 (0.84–0.92) | 0.83 (0.80–0.88) | 0.76 (0.75–0.80) |
| | 3 | 0.89 (0.87–0.94) | 0.88 (0.82–0.87) | 0.84 (0.82–0.90) | 0.79 (0.77–0.83) | 0.73 (0.71–0.76) |
| | 4 | 0.86 (0.84–0.91) | 0.84 (0.81–0.87) | 0.83 (0.80–0.87) | 0.76 (0.75–0.80) | 0.69 (0.67–0.70) |
| | 5 | 0.84 (0.80–0.88) | 0.82 (0.79–0.84) | 0.80 (0.77–0.82) | 0.74 (0.72–0.77) | 0.66 (0.63–0.68) |

Abbreviations: CI, confidence interval; HR, hazards ratio; Ref, reference

[a] From Cox proportional hazards regression; adjusted for age, height, body mass index, waist-hip ratio, smoking, physical activity, hormone replacement therapy use, education, family history, diabetes, total energy intake, total fat intake, dietary fiber intake, total fruits and vegetables intake, total red and processed meats intake, alcohol, and dietary oxidative balance score (see text).

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

[c] Categorized as took no supplemental minerals (category 1), and four categories of supplement scores among those who took supplemental minerals (categories 2 – 5), based on the supplement-only mineral score distribution.

[d] Categorized into five categories according to the diet-only mineral distribution.

[e] Reference category: participants who took no supplemental minerals and had low diet mineral scores.