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Mineral Intakes and Risk of Incident Colorectal Cancer

By

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MPH

Epidemiology

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Mineral Intakes and Risk of Incident Colorectal Cancer

By

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B.A.
Boston University
2015

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2017

Abstract

Mineral Intakes and Risk of Incident Colorectal Cancer

By Samyukta Swaminath

Previous epidemiologic findings suggest that mineral intakes may be associated with colorectal cancer risk. Other than for calcium, there are few reported epidemiologic studies on mineral intake-colorectal cancer associations, and the results for minerals, other than calcium, are inconsistent. Accordingly, we investigated associations of calcium, copper, iodine, iron, magnesium, manganese, phosphorus, potassium, selenium, sodium, and zinc intakes, separately and combined, with incident colorectal cancer.

We analyzed data from the Iowa Women's Health Study, a prospective cohort study of 41,837 55-69 year-old women, who completed a 127-item Willett food frequency questionnaire in 1986 and were monitored for cancer incidence via the State Health Registry of Iowa. After applying exclusion criteria, 35,221 women were available for analyses, including 1,744 who developed colorectal cancer during follow up. Participants' mineral intakes were ranked 1–5, with lower ranks indicating low mineral intakes and higher ranks indicating high mineral intakes, except for iron, copper, sodium, and phosphorus, 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 colorectal cancer association was estimated using multivariable Cox proportional hazards regression. For those in the highest relative to the lowest quintile of the mineral score, the hazard ratio was 0.75 (95% confidence interval: 0.73, 0.95; p-trend = 0.001).

These findings suggest that higher intakes of calcium, iodine, magnesium, manganese, potassium, selenium, zinc, combined with lower intakes of copper, iron, sodium, and phosphorus may be associated with lower risk of colorectal cancer among older women.

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Acknowledgements

Foremost, I would like to express my sincere gratitude to my advisor, Dr. Bostick for his continuous support, patience, and insightful comments. His immense knowledge and encouragement have been the driving force behind this thesis.

In addition, I would like to thank Dr. Caroline Um, for her advice and assistance in data analysis.

Lastly, I would like to thank my mother, Gayathri, for teaching me the importance of hard work and pushing me to be the best version of myself.

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CHAPTER I: BACKGROUND

Colorectal cancer (CRC) is the third most common cancer and the second most common cause of cancer-related deaths in the U.S. In 2017, there will be an estimated 95,520 new cases of colon cancer and 39,910 cases of rectal cancer diagnosed in the United States (1). Since 2000, incidence and mortality rates have declined among persons 50 years and older, primarily due to prevention and early detection of CRC through screening methods. In contrast, incidence and mortality rates among persons younger than 50 rose by 22% from 2000 to 2013. Additionally, CRC is expected to cause 50,260 deaths in 2017. The lifetime risk of developing CRC is 4.7% for men and 4.4% for women in the U.S (2).

The likelihood of a CRC diagnosis rises sharply after the age of 50. More than 90% of CRC cases occur in people who are 50 years or older. In men and women, the median age at diagnosis is lower for rectal cancers than for colon cancers. Women have a higher risk of developing right-sided (proximal) colon cancer than do men, who have a higher risk of developing left-sided (distal) colon cancer. Although the reasons for the sex-related differences are not yet completely understood, it most likely reflects the difference in exposure to hormones and other risk factors (3).

CRC incidence rates are highest among blacks, whose rates are about 25% higher than among whites, and lowest among Asian/Pacific Islanders, whose rates are 50% lower than those in the black population. Racial disparities in mortality may be attributed to being diagnosed at later stages of the disease, as a result of unequal access to screening. Other potential factors include socioeconomic status, leading to barriers to high quality cancer prevention, early detection, and treatment services. Thus, the racial disparities in CRC rates and outcomes may be attributable to differences in health-care utilization rather than biological differences (1).

Despite decreasing CRC incidence among adults 50 years of age and older, rates continue to increase in younger adults, especially for disease in the distal colon and rectum. Historically, CRC in younger adults has been associated with hereditary syndromes, particularly Lynch syndrome, which is primarily characterized by tumors on the right side of the colon. The reason(s) for increasing incidence in younger adults is unclear, but large increases in the incidence rates of obesity and diabetes in young adults may be contributing factors (4).

Worldwide, CRC represents 10.1% of all incident cancer in women and 9.4% in men. However, wide geographical variation in incidence exists in the global distribution of CRC. The highest estimated incidence rates are in Australia/New Zealand (44.8 and 32.2 per 100,000 in men and women, respectively). The lowest estimated incidence rates are found in Western Africa (4.5 and 3.8 per 100,000 in men and women respectively). This disparity suggests a possibility of the role played by Western lifestyle, in particular, Western dietary patterns. Over 63% of all cases are diagnosed in the developed world. Countries, such as the United States, Australia, and New Zealand, with the highest rates have up to 10-fold higher incidence than is found in countries in Africa and some parts of Asia, which have the lowest rates. Among migrants from low-risk to high-risk countries, incidence rates of CRC tend to resemble those typical of the population of the host country. This further supports evidence of environmental risk in CRC (5).

CRC rates vary within the United States as well. The pattern of CRC has dramatically changed over the past years. Rates were the highest in the Northeast and lowest in the Southeast in the 1950s and 1960s. However, the highest rates are currently in the Midwest and mid-South and lowest in the Northeast. Influences that have contributed to this disparity are regional variations of risk factors, access to screening and treatment,

socioeconomic factors, proximity to medical services, and legislative policies. After the mid-1970s, the 5-year survival rate for colon cancer has increased from 51% to 65%, with rectal cancer rates rising from 48% to 68%. The difference in overall survival between the two may be attributable to a higher probability of diagnosis at a localized stage in rectal cancer. The greatest improvement in 5-year survival is for the regional-stage disease, for which colon cancer survival rates increased from 55% to 73% and rectal cancer survival rates rose from 45% to 69%. This advancement is probably due to the progress in treating these patients, specifically 5-fluorouracil-based chemotherapy following surgery, which was advised by a National Institutes of Health expert panel in 1990 for stage III cancers (1).

Most CRC cases are sporadic non-familial cancers, associated with diet and other lifestyle associated factors. Approximately 5% of cases are caused by hereditary conditions, including familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome. Less common hereditary conditions include Peutz-Jeghers syndrome and juvenile polyposis (6).

Most sporadic cases begin as noncancerous growths in the colorectal epithelium, called adenomatous polyps or adenomas, which develop gradually over a period of 10 to 20 years. Approximately one-third to one-half of all individuals will develop at least one adenoma. Less than 10% of adenomas progress to invasive cancer. As the polyp increases in size, the likelihood of it evolving into cancer rises. Most colorectal cancers (96%) are adenocarcinomas, or cancer developing in glandular cells (7).

The extended period between the development of earlier abnormalities of polyps and of an invasive cancer makes diagnosis and removal of adenomatous polyps and early stage cancer via endoscopy a highly effective means of reducing CRC mortality. Among

asymptomatic individuals, at average risk for CRC, screening is recommended starting at 50 years (8).

CRC incidence has been associated with several nonmodifiable and modifiable risk factors. Nonmodifiable risk factors include age as previously discussed, personal medical history of chronic conditions, and family history of CRC or adenomatous polyps. Individuals with a first-degree relative who had CRC have up to 3 times the risk of developing the disease compared to people with no family history (9). If there is more than one affected relative or if a relative was diagnosed at a young age, the risk increases up to 6 times that of the general population. Approximately 20% of all CRC patients have had a close relative who was diagnosed with the disease. Having a family history of CRC has been associated with better survival, mostly because family members tend to be more aware and undergo screening. Those with a personal history of CRC are more likely to develop a subsequent cancer in the colon or rectum. Additionally, those with a history of adenomatous polyps have higher CRC risk, especially if a polyp is large or if there are multiple polyps. Although family history of adenomas appears to be associated with higher CRC risk, additional research is needed to confirm this. Individuals with chronic inflammatory bowel disease, with ulcerative colitis and Crohn disease being the most common, have a higher risk of developing CRC. Approximately 18% of patients with a 30-year history of ulcerative colitis will develop CRC (10). However, due to anti-inflammatory medications and improvements in screening to detect premalignant lesions, cancer risk in these patients has been lower in the last few years. Findings from studies, specifically observational cohorts, found a moderately higher risk of CRC among those with type 2 diabetes. Although type 2 diabetes and CRC share similar risk factors, such as obesity, high caloric diet, and sedentary lifestyle,

the association remains even after accounting for body mass index, waist circumference, and physical activity (11).

The major modifiable risk factors of CRC include obesity, physical activity, diet, postmenopausal hormones, tobacco, alcohol, and nonsteroidal anti-inflammatory drugs (NSAIDs) (10). Findings from prospective studies indicated that obesity, primarily assessed by body mass index (BMI), is associated with a higher risk of CRC. Those who are obese are about 30% more likely to develop CRC than are normal-weight individuals (12). Independent of BMI, visceral adiposity is directly associated with higher risk of CRC (13).

Physical activity, on the other hand, is associated with lower CRC risk. Biological mechanisms to support this association include decreasing insulin resistance, decreasing inflammation, decreasing intestinal transit time, reducing body fat, reducing hyperinsulinemia, and modulating immune function (14, 15). Findings from a systematic review of prospective cohort studies, indicated that routinely active individuals had a 21% lower risk of CRC compared to those who reported the least amount of physical activity (16).

The findings on hormone replacement therapy (HRT) and CRC among women have been consistent. In a meta-analysis of 18 observational studies, lower risk of CRC was observed among women who are long-term users of postmenopausal hormone therapy. The lower risk may be because HRT reduces DNA methylation of the estrogen receptors and related genes. However, postmenopausal hormones may be associated with higher breast cancer and cardiovascular disease risk and are therefore, not universally recommended (17).

Higher risk of colorectal adenomas is consistently observed among smokers. Approximately 7,000 to 9,000 deaths from CRC per year in the United States are attributable

to tobacco (18). There may be an induction period of 30 to 40 years between smoking and CRC. Free radicals in tobacco smoke increase blood and tissue markers of oxidative stress (19).

Epidemiological evidence indicates that high alcohol intakes increase CRC risk. Additionally, high alcohol intake has been consistently associated with higher risk of colorectal adenoma. Those with a lifetime average of 2 to 4 alcoholic drinks per day are estimated to have a 23% higher risk of CRC relative to those who consume less than 1 drink per day (20). Although the exact biological mechanism behind this association is unknown, hypotheses include the production of acetaldehyde through oxidation, which initiates irregular DNA methylation (21).

NSAIDs have consistently been associated with lower risk of CRC. Findings from an early analysis among men and women in the Cancer Prevention Study II cohort indicated that aspirin use at least 16 times a month was associated with a 40% lower risk for colon cancer mortality over a 6-year period (22). Similar findings were found in 7 cohort studies, which estimated that long-term aspirin use (approximately 20 years) may reduce the risk of CRC by 15% (23). In randomized controlled trials among FAP patients, NSAIDs, such as sulindac, celecoxib, and rofecoxib, reduced the mean size and mean number of colorectal polyps after 6 to 9 months of treatment. The proposed mechanism is that NSAIDs block COX-2 production, with catalyzes the production of prostaglandin E2, which promotes tumor epithelial cell proliferation, survival, and migration/invasion via multiple signaling pathways (24).

Diet plays an important role in colorectal carcinogenesis. Current evidence indicates that CRC risk may be associated with intakes of fruits and vegetables, red and processed meats, fiber, folate, vitamin D, and calcium (1).

There is inconsistent epidemiological evidence on the inverse association of fruit and vegetable intake and CRC risk. Although most studies, specifically case-control and retrospective studies, found an inverse association of fruit and vegetable consumption with CRC, several prospective cohort studies yielded inconsistent results (25-27). Findings from the Cancer Prevention Study II by the American Cancer Society found that men with a very low intake of vegetables and women with a very low intake of fruit were at a higher risk of colon cancer (26). Fruit and vegetable consumption has been hypothesized to provide protection through anticarcinogenic components, such as antioxidants (in particular, carotenoids, tocopherols, and vitamin C), folic acid, flavonoids, organosulfides, isothiocyanates, and protease inhibitors, that might reduce DNA damage, thus reducing mutations (27). Findings from a meta-analysis of 13 case-control studies indicated an inverse association between dietary fiber intake and CRC, although findings from prospective cohort studies do not support this association (28).

Red and processed meat is positively associated with CRC. Earlier prospective studies yielded inconsistent findings for the red meat intake and CRC risk association. However, findings from the prospective Health Professionals Follow-up Study and the Nurses' Health Study found a direct association between red meat intake and colon cancer risk (29, 30). Norat et al. found a dose-response association of red meat intake or processed meat intake: the estimated risk ratios (RR) for CRC were 1.24 (95% CI (confidence interval): 1.08, 1.41) for an increase of 120 g/day of red meat, and 1.36 (95% CI: 1.15, 1.61) for 30 g/day of processed meat (31). Findings from a meta-analysis of 19 prospective studies that included 8,000 cases indicated that individuals with the highest consumption of red and processed meat had a 28% and 20% higher risk of CRC respectively, relative to those with the lowest intakes (32). This positive association may be attributed to their high fat (and this high

energy) content and the formation of mutagenic heterocyclic aromatic amines during high temperature cooking (33). Additionally, red meat is a major source of heme iron, which catalyzes pro-oxidant reactions and promotes carcinogenesis by increasing cell proliferation in the mucosa through lipoperoxidation and/or cytotoxicity of fecal water (34).

An important nutritional factor in the pathogenesis of CRC, folate has been associated with a lower risk of CRC. Fifteen published retrospective epidemiologic studies that investigated the association of folate status (assessed by dietary folate intake or by the measurement of blood folate levels) with risk of CRC, collectively indicated approximately a 40% lower risk of colorectal neoplasms among those with the highest dietary folate intake relative to those with the lowest intake (35). Findings from a meta-analysis of 11 prospective studies that included 500,000 male and female participants, found a statistically significant inverse association of folate intake (dietary and supplemental) with risk of CRC (36). Furthermore, in the Nurses' Health Study, a 75% lower risk in CRC was found among women who took a multivitamin supplemental containing $\geq$ 400 μg of folic acid for at least 15 years compared with those not taking folic acid (37). However, in a large randomized controlled trial consisting of 987 adults with a history of precancerous colon polyps, folic acid increased adenomas, especially advanced adenomas (144). Various endogenous forms of folate are essential for DNA methylation, synthesis, and repair. Proposed mechanisms include low folate levels limiting the supply of methyl groups needed for DNA methylation. The low levels can also cause large assimilation of uracil, leading to increased number of chromosomal breaks. The folate deficiency may lead to DNA hypomethylation, which is an early event in colon carcinogenesis (36).

Currently, an inverse association of vitamin D with CRC is consistent. In the Iowa Women's Health Study and the Health Professionals Follow-Up Study, total vitamin D was

inversely associated with CRC risk. Stronger associations were found when supplemental or total (dietary and supplemental) were considered (38). Furthermore, case-control studies also found inverse associations of circulating 25(OH) vitamin D levels and colorectal adenomas (39-41). A systematic review of 18 observational studies found that an intake of 1000 IU/day of Vitamin D was associated with 50% lower risk of CRC incidence than is found in the general reference population (42). As an underlying mechanism, vitamin D is thought to protect against colorectal neoplasia by inhibiting proliferation, inducing differentiation, inhibiting angiogenesis, and promoting apoptosis in epithelial tissues. Additionally, it regulates homeostasis of intestinal epithelium by inhibiting tumor-promoting inflammation. It also regulates more than 200 genes, including genes responsible for the regulation of cellular proliferation, differentiation, angiogenesis and immunomodulatory activities (43). Vitamin D also may have synergistic chemopreventaive effects with calcium against colorectal neoplasia (38).

The risk of CRC may be influenced by dietary and supplemental intake of minerals. High calcium intake is associated with lower risk of CRC. In animal models, higher dietary calcium inhibited large-bowel carcinogenesis (44). Additionally, calcium supplementation trials for adenoma prevention found reduced adenoma recurrence (45). Findings from a pooled analysis of 10 cohort studies, that assessed dietary consumption and total calcium intake (diet and supplementation) reported 10% to 15% lower risk for CRC (46). A randomized, double-blind, placebo-controlled trial that involved 36,282 postmenopausal women, found that daily supplementation of calcium with vitamin D for seven years had no effect on the incidence of CRC (48). However, calcium doses as well as vitamin D doses used may have been insufficient to demonstrate a protective effect, particularly given the fraction of participants who were not fully adherent throughout the study. There are two

possible mechanisms for the protective effect of calcium. Calcium binds to bile acids and free fatty acids, which diminishes their proliferative effect on the colon mucosa. It is involved in the modulation of the APC colon carcinogenesis pathway through mediating E-cadherin and β-catenin expression via the calcium-sensing receptors. Another hypothesis, based on in vitro studies in human epithelial cells, is that calcium directly inhibits proliferation of colonic epithelial cells and induces terminal differentiation (49).

Abundant in numerous foods, magnesium is involved in various biochemical reactions that modulate cell functions and plays a crucial role in genetic stability and DNA synthesis (50). Supplemental magnesium reduced CRC tumorigenesis in animal experiments and inhibited c-myc oncogene expression in colon cancer cells (51, 52). A randomized control study reported that magnesium treatment decreased fasting C-peptide concentrations, a marker for insulin secretion, which is associated with a higher risk of CRC in humans (53). Among postmenopausal women in the Iowa Women's Health Study cohort, an inverse association of magnesium intake with colon cancer but not rectal cancer was observed (54). On the other hand, a Swedish study based on a prospective cohort of older women aged 40 to 75 years, indicated that high magnesium intake may be inversely associated with the occurrence of both colon and rectal cancer in women (55). Although 3 out of 7 of observational studies support an inverse effect of magnesium with colorectal cancer (54-55, 98), whereas the other 4 have found no associations (52, 99-101). Findings from a Netherlands Cohort Study found that magnesium intake was weakly nonsignificantly and inversely associated with CRC risk among men and women (52). A suggested underlying biological mechanism is that magnesium may reduce oxidative stress, improve insulin sensitivity, or otherwise decrease colonic epithelial cell proliferation (52). Calcium, an antagonist of magnesium, competes with magnesium for intestinal absorption and transport,

suggesting that, the ratio of calcium to magnesium intake may be a key factor in colorectal carcinogenesis. In a case-control study (n=2,204), an inverse association of magnesium with risk of colorectal adenoma was found only among those with a low ratio of calcium to magnesium intake (56).

Both an antioxidant and pro-oxidant, copper binds to proteins and is involved in structural and catalytic properties of enzymes in oxidation processes (57, 58). Dietary copper deficiency may increase susceptibility to oxidative damage, leading to cancers (58-60). Ingestion of a diet deficient in copper in rats increased the formation of 3,20 -dimethyl-4-aminobiphenyl and dimethyl hydrazine-induced aberrant crypt foci, which are precursor lesions from which adenomas and adenocarcinomas develop (61). The epidemiologic studies that reported copper and CRC associations yielded inconsistent results. A case-control study (n = 171 CRC cases, n = 309 controls) in France reported a higher risk of CRC with higher copper intake (OR (odds ratio) = 2.4, 95% CI: 1.3, 4.6) (62). Another hospital-based case control study (n = 822 cases, n = 926 controls) conducted in Hong Kong reported that copper was independently protective against colon cancer (63).

Zinc, an essential component of an antioxidant enzyme, is involved in several cellular functions, such as DNA repair and apoptosis (64, 65). Few epidemiologic studies reported on a possible antioxidant role of zinc. In the Iowa Women's Health Study, a prospective cohort of postmenopausal women, dietary zinc intake was associated with a lower risk of colon cancer. The inverse association was stronger among women who consumed alcohol than among those who did not (66). A population-based prospective cohort in Japan reported that zinc intakes were not significantly associated with CRC risk. However, an inverse association between zinc intake and CRC risk among drinkers in men was found. (67)

Although the pro-oxidant, iron, is thought to be carcinogenic, epidemiologic evidence regarding its association with CRC remains inconclusive (68). Two forms of dietary iron are heme iron from red meat and non-heme iron from plants and dairy products. Heme iron is thought to contribute to colorectal carcinogenesis by promoting free radical production and lipid peroxidation (69). A meta-analysis of 5 prospective cohorts including 566,607 individuals, found high intake of heme iron to be associated with higher risk of colon cancer. The study suggested adjusting for calcium intake when assessing the association of iron intake with CRC risk because calcium can inhibit the heme iron induced cytotoxicity (70). Fifteen studies, which included seven case-control studies, two ecological studies, and five cohort studies, investigated the association of iron intake with CRC risk. Twelve of these studies found a positive association between dietary iron and CRC (62, 66, 71-79), while the remaining studies found no significant direct association between dietary iron intake and CRC risk (80).

Selenium is a trace element that is a part of important antioxidant selenoproteins, such as such as glutathione peroxidase, selenoprotein P, and thioredoxin reductases. It is inversely associated with markers of oxidative stress and DNA damage (81). In an analyses of pooled data from three prospective studies, Jacobs et al. found that subjects with baseline serum or plasma selenium in the highest quartile had a significantly lower risk of adenoma recurrence (OR = 0. 66, 95% CI: 0.50, 0.87) relative to those in the lowest quartile (82). A cross–sectional study (n = 803) indicated an inverse association of blood levels of selenium with colorectal adenomas (83). A randomized, double-blind, placebo-controlled trial (n = 1312) that involved supplementation with 200 μg of selenium per day or a placebo for prevention of nonmelanoma skin cancer, found a 58% reduction in CRC incidence in the secondary analyses of the data (84). Underlying mechanisms include selenium's antioxidative properties,

which may decrease reactive oxygen species exposure induced by androgens, ageing, or microbial gut flora, therefore reducing CRC risk (81).

Phosphorus, a component of phospholipids, is rapidly absorbed as hormonal mechanisms attempt to maintain the serum inorganic phosphate concentration within narrow limits. However, exposure of cells to a brief high-serum inorganic phosphorus concentration can potentially signal alterations in cell functions that lead to deleterious affects (85). Although epidemiologic studies with phosphorus and CRC are sparse, few studies investigated a possible modulating effect of phosphorus on the association of calcium with CRC. A French case-control study (n = 154 small adenoma subjects, n = 208 large adenoma subjects, n = 426 polyp-free subjects, n= 171 cancer cases, and n=309 population controls) that assessed associations of calcium and phosphorus with CRC found that high dietary intake of phosphorus or a low calcium to phosphorus ratio were not associated with a higher risk of adenomas whatever their size. Higher risk with phosphorus intake was found in women, but not in men (86). A French prospective cohort of 100,000 women, found phosphorus to be inversely associated with adenoma risk (RR = 0.70, 95% CI: 0.54, 0.90) (87).

Epidemiologic data on potassium, manganese, iodine, and sodium remain inconclusive and sparse. Two case-control studies in France found lower colon cancer mortality with higher potassium intake (88, 89). Although the exact biological mechanism is unknown, it is hypothesized that dysregulated potassium channels may initiate tumorigenesis (90). Manganese is an essential component of manganese SOD, an antioxidant enzyme that protects mitochondria from oxygen radical damage (91), suggesting that manganese may lower risk of CRC. Iodine, an antioxidant, is increasingly being acknowledged for its pro- and anti-carcinogenic properties (92). Although the exact mechanism is unclear,

electrogenic sodium absorption, located mainly in the apical membrane of surface colonocytes, is present throughout the colon. Additionally, colonic crypts exhibit Na+ dependent net water absorption (145-147). Also, aldosterone promotes sodium reabsorption as an electrogenic sodium transport. When sodium levels are high, aldosterone is unable to be suppressed, which may lead to cell proliferation via G protein- coupled estrogen receptor (148-149). Also, high sodium intake decreases 11β-hydroxysteroid dehydrogenase type 2 activity in the colonic epithelium, slowing down cortisol catabolism (150). This suggests that high sodium intake could impair immune defenses in the colon epithelium. (150).

Research is still ongoing on the role of specific mineral components in CRC risk. A limited number of studies have investigated the association between specific minerals and CRC risk. In addition, the exact mechanisms underlying the effects of the minerals on colorectal carcinogenesis and the optimal levels of exposure to reduce risk of colorectal cancer remain unclear. To our knowledge, this is the first study to investigate a mineral score, to account for the combined effects of calcium, copper, iodine, iron, magnesium, manganese, phosphorus, potassium, selenium, sodium, and zinc intakes, in relation to colorectal cancer incidence.

CHAPTER II: MINERAL INTAKES AND RISK OF INCIDENT COLORECTAL CANCER

Abstract

Previous epidemiologic findings suggest that mineral intakes may be associated with colorectal cancer risk. Other than for calcium, there are few reported epidemiologic studies on mineral intake-colorectal cancer associations, and the results for minerals, other than calcium, are inconsistent. Accordingly, we investigated associations of calcium, copper, iodine, iron, magnesium, manganese, phosphorus, potassium, selenium, sodium, and zinc intakes, separately and combined, with incident colorectal cancer.

We analyzed data from the Iowa Women's Health Study, a prospective cohort study of 41,837 55-69 year-old women, who completed a 127-item Willett food frequency questionnaire in 1986 and were monitored for cancer incidence via the State Health Registry of Iowa. After applying exclusion criteria, 35,221 women were available for analyses, including 1,744 who developed colorectal cancer during follow up. Participants' mineral intakes were ranked 1–5, with lower ranks indicating low mineral intakes and higher ranks indicating high mineral intakes, except for iron, copper, sodium, and phosphorus, 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 colorectal cancer association was estimated using multivariable Cox proportional hazards regression. For those in the highest relative to the lowest quintile of the mineral score, the hazard ratio was 0.75 (95% confidence interval: 0.73, 0.95; p-trend = 0.001).

These findings suggest that higher intakes of calcium, iodine, magnesium, manganese, potassium, selenium, zinc, combined with lower intakes of copper, iron, sodium, and phosphorus may be associated with lower risk of colorectal cancer among older women.

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer-related deaths in the U.S. (1, 102-103). Findings from epidemiologic studies indicate that environmental factors play an important role in colorectal cancer risk (104, 18), diet and physical activity being the strongest environmental risk factors for the disease (105-109).

Epidemiologic findings suggest that mineral supplement intakes may be associated with lower risk of colorectal cancer (110-112). Other than for calcium, there have been few observational studies on associations of mineral intakes with colorectal cancer risk, and the results for minerals other than calcium have been inconsistent. Higher intakes of calcium have generally been associated with a lower risk of colorectal cancer incidence in observational studies (113-116). There are two possible mechanisms for a protective effect of calcium. Calcium binds to bile acids and free fatty acids, which diminishes their mitogenic and mutagenic effects on the colon mucosa. Another hypothesis, based on in vitro studies, is that calcium directly inhibits proliferation and induces terminal differentiation of colonic epithelial cells (49). Involved in various biochemical reactions, magnesium modulates cell functions and plays a crucial role in genetic stability and DNA synthesis (50). Supplemental magnesium was found to reduce CRC incidence in animal experiments and inhibited c-myc oncogene expression in colon cancer cells (51, 52). Although three out of seven observational studies found an inverse association of magnesium with CRC (54-55, 98), other studies found no inverse associations (52, 99-101). Calcium, an antagonist of magnesium, competes with magnesium for intestinal absorption and transport, suggesting that the ratio of calcium to magnesium intake may be a consideration in CRC carcinogenesis. In a case-control study (n=2,204), an inverse association of magnesium with risk of colorectal adenoma was found only among those with a low ratio of calcium to magnesium

intake (56). Both an antioxidant and pro-oxidant, copper is required for the structural and catalytic properties of important enzymes, such as copper-zinc superoxidase dismutase (an antioxidant enzyme) (57-59), but also generates reactive oxygen species by the Fenton reaction (117). Few epidemiologic studies reported copper and CRC associations and yielded inconsistent results. A case-control study in France observed a higher risk of CRC with higher copper intake (62).

Due to its high oxidative potential, iron has been proposed as a risk factor in colorectal carcinogenesis (68). The findings from epidemiologic studies on an association of total iron intake with colorectal cancer risk have been inconsistent (80, 82, 118-120). A meta-analysis of 5 prospective cohorts including 566,607 individuals, found an association between high intake of heme iron and higher risk of colon cancer (70). However, the carcinogenic potential of iron in colorectal cancer remains unclear (68). Few epidemiologic studies reported on a possible antioxidant role of zinc. In the Iowa Women's Health Study, a prospective cohort with postmenopausal women, intake of dietary zinc was associated with a lower risk of colon cancer (77). Epidemiologic data on phosphorus, selenium, potassium, manganese, sodium, and iodine remain sparse and inconclusive (61, 83-89, 92, 93-95, 96). Inconclusive results may be due to the close interactions among minerals. For example, some data suggest that a high calcium relative to magnesium intake may exaggerate magnesium deficiency and, in turn, lead to risk of colorectal cancer (56). Comparable patterns of synergisms and antagonisms are found between copper and iron, and copper and zinc (121).

Few studies have investigated associations of specific minerals, other than calcium, with CRC risk, and to our knowledge, none considered the aggregate effects of minerals in the diet. Accordingly, we examined associations of intakes of calcium, copper, iodine, iron,

magnesium, manganese, phosphorus, potassium, selenium, sodium, and zinc with risk of colorectal cancer incidence separately and combined in a prospective cohort.

Methods

The Iowa Women's Health Study, established in 1986, is a prospective cohort study of cancer incidence and mortality among post-menopausal Iowa women. The site for this cohort study, Iowa, was selected due the availability of cancer incidence and mortality data from the State Health Registry of Iowa, a participant in the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. The subjects were selected from the 1985 current drivers list from the Iowa Department of Transportation. A total of 195,294 women ages of 55-69 years were potentially eligible for this study. From this sampling pool, a 50 percent random sample was selected, resulting in 99,829 women. One hundred three women were excluded because their mailing addresses were not in Iowa. The remaining 99,826 women were mailed a questionnaire, with a postcard sent 1 week later and letter sent 4 weeks later as follow ups to prompt the questionnaire return. Of these women, 1,797 were determined to be ineligible because they were out of the age range, male, died before the questionnaire arrived, or had a confirmed address outside of Iowa. A total of 41,836 women were enrolled (of 98,029 eligible; 42.7% questionnaire return rate).

Respondents and non-respondents were compared based on drivers' license and county information; the respondents were on average 3 months older and had a slightly lower body mass index. Respondents were more likely to reside in more rural counties and, on average, had a lower income and education level than the non-repondents. Cancer incidence, however, was not considerably different between the two groups.

The baseline survey included questions on diet, family and personal history, reproductive history, smoking, physical activity, weight, height, and demographic information. Written instructions and tape measures were provided so that the respondent could have someone measure their waist circumference (1 inch above the umbilicus) and hip

circumference (maximal protrusion); waist-hip ratio was calculated using these measurements. Body mass index (BMI) was calculated as self-reported weight over self-reported height squared (kg/m^2). The dietary portion was an adaptation of the Willett 127-item semi-quantitative food frequency questionnaire (FFQ). Participants reported their frequency of consumption among nine categories, with a commonly used serving size specified, from never or <1 serving/month to ≥ 6 servings/day. Part of the food frequency questionnaire included intakes and dosages of multivitamin, vitamin, and mineral supplements. Daily nutrient intakes were calculated by multiplying the frequency of consumption of the specific unit of each food by the nutrient content of the respective food item (122, 123).

Follow-up questionnaires, mailed in 1987, 1989, 1992, 1997, and 2004, included similar questions except that education, place of residence, and waist hip circumferences were not re-assessed. Respondents and non-respondents who were alive at baseline and continued to reside in Iowa were followed for the occurrence of cancer or death through the State Health Registry of Iowa. New cancer cases and deaths were identified via a computer match performed between the Registry and the cohort based on name, birth date, zip code, and social security number (122, 123). Colorectal cancer was defined as adenocarcinoma of the colon or rectum (ICD-O codes: 18.0-18.9, 18.0-19.9, and 18.0-20.9).

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. For each respondent, the total number of person-years was calculated starting with the date of entry into the study. For cases, person-years ended at the date of diagnosis of colorectal cancer. For non-cases who died during follow-up, person-years were accrued to

the date of death using mortality data from Iowa death certificates or the National Death Index. Individuals who were known to have left Iowa were censored since they were considered lost to follow up by the State Health Registry of Iowa. For the non-cases who had registered a change of address outside of Iowa with the National Change of Address System, person-years were accumulated to the date of moving. For non-cases whose responses indicated a move out of Iowa in the 1987 follow-up questionnaire, person-years were accumulated to the midpoint between the time of their entry into the study and the time of the follow-up questionnaire (122, 123).

Of the 41, 836 enrolled individuals, women who had reported previous cancers at baseline other than non-melanoma skin cancer were excluded (n=3,830) from the present analysis. The total cohort at risk for incident colorectal cancer was 38, 006 women. Women were also excluded if they left 30 or more items blank on the food frequency questionnaire (n=2,499), and if their responses resulted in implausibly high or low total daily energy intakes (<600 or >5,000 kcal/day) (n=286). The cut point for the number of blank items on the questionnaire was chosen such that any participant who skipped an entire page of the questionnaire was excluded. After these exclusion criteria were applied, 35,221 women were available for analyses.

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 were considered statistically significant. The FFQ-derived food and supplement data were used to calculate mineral scores for all participants. The mineral score included total (dietary plus supplemental) intakes calcium, copper, iodine, iron, magnesium, manganese, phosphorus, potassium, selenium, sodium, and zinc, and supplemental intakes only of selenium and iodine. Nutrient density intakes were calculated as the intake of a

mineral per 1,000 kilocalories of total energy intake per day. The mineral score for each individual was ranked from a scale of 1 through 5, with lower ranks indicating low mineral intakes and higher ranks indicating higher mineral intakes, except that for iron, copper, sodium, and phosphorus, the rankings were reversed to account for their pro-oxidant properties. The mineral score for each woman was the sum of her respective ranking of each mineral.

Selected participant characteristics at baseline across quintiles of the mineral score were summarized and compared using χ^2 tests. The association of the mineral score with risk of incident colorectal cancer was estimated using Cox proportional hazards regression models to calculate hazard ratios and their 95% confidence intervals (HR; 95% CI). The covariates, chosen *a priori* as previously having been found to be strong risk factors for colorectal cancer, included age, total energy intake, height, BMI, waist-hip ratio, smoking, physical activity, hormone replacement therapy (HRT) use, education, family history, diabetes, total fat intake, total fiber intake, total fruit and vegetable intake, red and processed meat intake, alcohol, and a dietary oxidative balance score. An equal-weight dietary oxidative balance score (OBS), as described by Dash et al., included the dietary anti-oxidants such as alpha-carotene, beta-carotene, beta-crypotoxanthin, lutein, lycopene, vitamin C, vitamin E, omega fatty acids, and flavonoids, and the dietary pro-oxidants iron, omega-6 fatty acids, and saturated fat (125). A linear 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 colorectal cancer incidence according to selected covariate values. Strata for the following continuous variables were created based on values above and below the population median: age, height, waist-hip ratio, dietary OBS,

total energy, total fat, dietary fiber, total fruits and vegetables, and 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 colorectal cancer 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 colorectal cancer sites. Incident CRC in the cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, and overlapping colon lesions (ICD-O codes 18.0-18.6, 18.8-18.9), were categorized as proximal colorectal cancer (n = 1,064, 61% of total cases), and cancers located in the sigmoid colon, rectosigmoid junction, and rectum (ICD-O codes 18.7, 19.9, 20.9) were categorized as distal colorectal cancer (n = 680, 39% of total cases). There were no cases with missing codes or unspecified subsites.

Several sensitivity analyses were conducted. First, individual mineral components were removed from the mineral score and replaced one at a time to assess whether any individual component was particularly influential in the association of the score with CRC. To reduce ambiguity for a temporal relation between the mineral score and incident colorectal cancer, we excluded participants who were diagnosed with colorectal cancer 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 1. Study participants were, on average, 61 years of age, and 98% were Caucasian. Those in the higher mineral score quintiles tended to be less educated, and more likely to have diabetes, a normal body-mass index, a smaller waist-hip ratio, and a higher level of physical activity than those in the lower quintiles. On average, participants in the upper relative to the lower quintiles had higher intakes of total fat, dietary fiber, and total fruits and vegetables, and lower total energy and red and processed meats intakes.

The associations of the mineral score with risk of incident colorectal cancer estimated using Cox proportional hazards regression models are summarized in Table 2. Adjustment for multiple known and suspected risk factors had a minimal effect on the risk estimates. In the multivariable-adjusted analysis, for each one point increase in the mineral score, there was an estimated statistically significant 2% lower risk for incident colorectal cancer. 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 for colorectal cancer in the multivariable analysis.

In sensitivity analyses, exclusion of those who died or were diagnosed with colon cancer during their first year of follow up had negligible impact on the risk estimates (Table A.1). Similarly, censoring participants when they reached age 75 had no substantial impact on our primary findings (Table A.1). Also, risk estimates after the removal and replacement of each score component one at a time differed only minimally from those with the full score (Table A.2). Also, we found no substantial or consistent differences in our findings according to colon site (Table A.5). Similarly, we found no consistent or substantial

differences in the associations according to levels of the other risk factors noted in the statistical section (Table A.4).

Discussion

Our findings suggest that higher intakes of calcium, iodine, magnesium, manganese, potassium, selenium, and zinc, combined with lower intakes of copper, iron, sodium, and phosphorus may be associated with lower risk of incident colorectal cancer. To our knowledge, ours is the first epidemiological study on an association of a mineral score comprising these mineral intakes with incident colorectal cancer.

There is biologic plausibility and animal experimental evidence for protection against colorectal adenomas by higher intakes of calcium, magnesium, selenium, zinc, iodine, manganese, and potassium, and lower intakes of copper, iron, phosphorus, and sodium. The proposed mechanisms for calcium include binding 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 (126), and inhibition of proliferation and inducing terminal differentiation (49). The proposed mechanisms for magnesium include reducing oxidative stress by improving insulin sensitivity (52), maintaining genome stability (127), and preventing mutations in colonic epithelial cells (128). Underlying mechanisms for selenium include its antioxidant properties, which decrease reactive oxygen species induced by androgens, ageing, or microbial gut flora (83). Selenium is an essential component of glutathione peroxidase, an antioxidant enzyme that catalyzes the breakdown of hydrogen peroxide to water and organic hydroxyperoxides to alcohol. An antioxidant, iodine, acts as an electron donor and reduces free radicals. Also, it indirectly renders amino acids, such as tyrosine and histidine, and fatty acids, such as arachadonic acid, less oxidized through iodination (129). Manganese is an essential component of manganese SOD, an antioxidant enzyme that protects mitochondria from oxygen radical damage (96). Although the exact biological mechanism of potassium is unknown, it is hypothesized that

dysregulated potassium channels may initiate tumorigenesis (92). Proposed mechanisms for zinc include inhibition of NADPH oxidases and suppression of the proliferation of colorectal cancer cells through activation of extracellular signal regulated kinases (130). Also, zinc along with copper, is an essential component of the antioxidant enzyme, Cu, Zn-SOD (57-59). Additionally, copper is both an antioxidant and pro-oxidant. On the one hand, it binds to proteins and is involved in structural and catalytic properties of enzymes in oxidation processes (57, 58). On the other hand, chronic copper overload may also lead to oxidative stress conditions (65). Due to its high oxidative potential, iron has been proposed as a risk factor in colorectal carcinogenesis. Heme iron is thought to promote carcinogenesis by increasing cell proliferation in the mucosa through lipoperoxidation and/or cytotoxicity of fecal water (34). High sodium intake decreases 11β-hydroxysteroid dehydrogenase type 2 activity in the colonic epithelium, slowing down cortisol catabolism (150). This suggests that high sodium intake could impair immune defenses in the colon epithelium. Phosphorus, a component of phospholipids, is rapidly absorbed as hormonal mechanisms attempt to maintain the serum inorganic phosphate concentration within narrow limits. However, exposure of cells to a brief high-serum inorganic phosphorus concentration can potentially signal alterations in cell functions that lead to deleterious affects (87). Also, phosphate, which contains phosphorus, binds calcium, thus preventing calcium from binding to bile acids.

Our findings are consistent with much of the data available from previous studies on intakes of calcium, iodine, magnesium, manganese, potassium, selenium, zinc, sodium, copper, iron, phosphorus and colorectal cancer risk. Our findings of decreasing risk of colorectal cancer with an increasing mineral score supports the anti-oxidative and other anti-colon carcinogenic effects of calcium, iodine, magnesium, manganese, potassium, selenium,

and zinc, and the pro-oxidative and other pro-colon carcinogenic effects of copper, iron, sodium, and phosphorus. To our knowledge, there are no previous reports of associations of combined intakes of calcium, iodine, magnesium, manganese, potassium, selenium, sodium, zinc, copper, iron, and phosphorus with colorectal cancer incidence. However, a few studies investigated associations of limited combinations of certain minerals with CRC. In a case-control study (adenoma cases = 688, hyperplastic polyp cases=210, and polyp-free controls=1,306), it was found that total magnesium consumption was statistically associated with a lower risk of colorectal adenoma, primarily among individuals with a low calcium: magnesium intake ratio (56). Findings from animal models suggested that a diet low in copper, low in manganese, and high in iron were associated with the formation of aberrant crypt foci, which are preneoplastic lesions for colon cancer. The lowest number of aberrant crypt foci was observed in rats fed adequate dietary copper and dietary manganese, whereas the highest number of aberrant crypt foci was observed in those fed low copper/low manganese diets (61). Findings from a French case-control study (cases: n=171, controls: n=309) suggested that high energy, copper, iron, and vitamin E intakes were individually associated with higher risk of colorectal cancer (62). In a prospective cohort study (n=34,708) of postmenopausal women, heme iron was associated with a positive trend for colon cancer incidence within each category of zinc; however, zinc was inversely associated with colon cancer incidence within each category of heme iron (75). Findings from a French prospective cohort (n=73,034), found no association of a calcium to phosphorus ratio with colorectal tumor risk (89).

Other than for calcium, there have been few observational studies on associations of individual mineral intakes with colorectal cancer risk, and the results for minerals other than calcium have been inconsistent. Findings from a meta-analysis of 13 epidemiologic studies

indicated that high calcium intake was associated with lower colorectal cancer risk (RR = 0.92, 95% CI: 0.89, 0.95) (141). Furthermore, in a meta-analysis of 24 prospective cohort studies, an inverse CRC association was found with calcium (RR = 0.92, 95% CI: 0.70,0.92) (142). Three of seven observational studies found an inverse association of magnesium with CRC (52, 54-55, 98-101). The reported findings from epidemiologic studies on an association of total iron intake with colorectal cancer risk are inconsistent (80, 82, 118-120). Few epidemiologic studies reported on a possible zinc-colon cancer association. In the Iowa Women's Health Study, solely dietary zinc intake was associated with a lower risk of colon cancer (75). Epidemiologic data on phosphorus, selenium, potassium, manganese, and iodine remain sparse and inconclusive (61, 83-89, 92, 96).

Although a combined mineral score has not been previously reported, other similarly constructed scores have been used. Oxidative balance scores, comprised of anti- and pro-oxidant exposures, have been used to investigate an association of oxidative balance with risk of colorectal neoplasms (135, 136). Researchers have also developed inclusive dietary scores or indexes, which incorporate multiple foods and nutrients to assess the overall dietary intake and their association with disease outcomes (138). Associations of a dietary inflammatory index (DII), a score composed of multiple putative dietary anti- and pro-inflammatory exposures, with colorectal cancer, other cancers, and other chronic diseases have been reported, all of which suggested higher risk with a more pro-inflammatory score (131-134). In order to incorporate the synergistic effects of food items present in the Mediterranean diet, the Mediterranean diet score (MDS) has been used to investigate an association of the Mediterranean diet with colorectal cancer and cardiovascular disease (137). The Healthy Eating Index (HEI), a score based on recommendations from MyPyramid and

the US Dietary Guidelines for Americans, has been used to investigate an association of that diet pattern with CRC risk (139, 140).

A strength of this study was the novel composite mineral score used to summarize mineral exposures. Whereas the effects of individual minerals on risk for colorectal cancer 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 GI 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 (69, 143). 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 colorectal cancer diagnosis; data on many potential confounding variables; the use of cancer incidence, rather than mortality, as the endpoint of interest; and the use of a validated dietary assessment instrument.

Study limitations include the known limitations of food frequency questionnaires and measuring diet only once. Another limitation was the possible overestimation of fruit and vegetable intake; the reported average consumption of all fruit and vegetable in this cohort

was 37.8 serving per week or 5.4 servings per day. Also, the study population consisted only of white women; thus, generalization to men, other populations, or races may be limited. Additionally, 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 colorectal cancer 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 intakes of calcium, iodine, magnesium, manganese, potassium, selenium, and zinc, combined with lower intakes of copper, iron, sodium, and phosphorus may be associated with lower risk of colorectal cancer.

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Table 1. Selected participant characteristics at baseline across quintiles of the mineral score[a]; Iowa Women's Health Study, 1986-2012

Characteristics[b]	Mineral Score				
	Quintile 1: < 15	**Quintile 2: 15 - 16**	**Quintile 3: 17 - 18**	**Quintile 4: 19 - 20**	**Quintile 5: 21 - 30**
	Median = 12	**Median = 15**	**Median = 17**	**Median = 18**	**Median = 21**
	(N = 5,369)	**(N = 6,464)**	**(N = 7,637)**	**(N = 7,287)**	**(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)
Level of 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	16.4	16.2	15.1	14.1	13.8
Former	15.4	16.5	18.0	20.8	24.4
Current	68.2	63.1	67.0	65.1	61.8
Alcohol intake (%)					
None	59.6	56.3	54.7	54.5	51.8
> 0 g/day - < 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)

Characteristics[b]	Mineral Score				
	Quintile 1: <15 Median = 12 (N = 5,369)	**Quintile 2: 15 - 16 Median = 15 (N = 6,464)**	**Quintile 3: 17 - 18 Median = 17 (N = 7,637)**	**Quintile 4: 19 - 20 Median = 18 (N = 7,287)**	**Quintile 5: 21 - 30 Median = 21 (N = 8,464)**
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)
Total fruit and vegetable intake (servings/week)	39.1 (22.3)	41.1 (21.1)	44.8 (25.7)	47.7 (32.5)	47.5 (24.6)
Red and processed meat intake (servings/week)	8.7 (7.2)	8.1 (5.3)	7.1 (5.0)	6.0 (4.1)	4.8 (3.1)

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

Table 2. Associations[a] of the mineral score[b] with risk for incident colorectal cancer among older women; Iowa Women's Health Study, 1986-2012

	# cases	Age- and total energy intake-adjusted associations (HR, 95% CI)	Multivariable-adjusted[c] associations (HR, 95% CI)
Mineral score continuous	1,744	0.99 (0.95, 1.00)	0.98 (0.96, 1.00)
Mineral score quintiles (median)			
1 (12)	286	1.00 (referent)	1.00 (referent)
2 (15)	346	0.96 (0.82, 1.13)	0.91 (0.89, 1.10)
3 (17)	367	0.84 (0.72, 0.98)	0.86 (0.79, 0.97)
4 (18)	365	0.87 (0.77, 1.02)	0.87 (0.77, 0.99)
5 (21)	380	0.77 (0.67, 0.91)	0.75 (0.73, 0.95)
P-trend		*0.001*	*0.001*

Abbreviations: HR, hazards ratio; CI, confidence interval

[a] From Cox proportional hazards regression

[b] Mineral score 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] 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, total fiber intake, total fruit and vegetable intake, red and processed meat intake, alcohol, and dietary oxidative balance score (see text)

CHAPTER III: SUMMARY AND FUTURE DIRECTIONS

We investigated associations of minerals, such as iron, iodine, magnesium, manganese, zinc, selenium, calcium, potassium, sodium, phosphorus, and copper, individually and combined with risk of colorectal cancer. We constructed a composite mineral score to represent higher intakes of calcium, iodine, magnesium, manganese, potassium, selenium, and zinc, and lower intakes of copper, iron, sodium, and phosphorus. Our findings suggest that a higher mineral intake score may be associated with lower risk of incident colorectal cancer. While our findings require confirmation by other well-designed large studies, they support potential benefits of increasing consumption of most minerals and decreasing consumption of iron, copper, sodium, and phosphorus in reducing risk for colorectal cancer incidence.

While our study indicates promising associations between a composite mineral score and colorectal cancer incidence, additional studies are required before establishing the beneficial or harmful effects of minerals with regard to colorectal cancer and other chronic diseases. Additional large prospective studies using a similar combined scoring method to account for the inter-correlations among several minerals are needed. The efficacy and safety of mineral supplementation for the prevention of colorectal cancer needs to be tested in a randomized trial. Intervention studies are required to clarify whether minerals other than calcium reduce risk of colorectal cancer incidence. However, the duration and timing of mineral interventions with respect to colorectal cancer etiology may be difficult to determine. The potential beneficial or adverse effects of mineral supplements in colorectal cancer patients warrant further study. Also, studies of the development of advanced cancer according to long-term supplement use in individuals initially cancer-free may provide information on the benefits or harms of minerals and colorectal cancer incidence. Studies

should consider those with cancer separately from those who are cancer-free since a mineral may initially have anti-carcinogenic properties before tumor development, but later accelerate tumor growth. Additionally, studies should focus on possible modes of action of selected minerals, such as potassium, sodium, manganese, iodine, and others, whose role in the modulation of colorectal tumorigenesis remains relatively unknown. Randomized controlled trials will help establish whether or not there is a role of minerals in colorectal carcinogenesis.

To the best of our knowledge, a mineral score such as ours has not been investigated in relation to any disease other than colorectal cancer. We would like to investigate our mineral score in relation to other diseases linked to minerals, such as cardiovascular diseases, diabetes, prostate cancer, and breast cancer. Since our population was limited to white women, replication of our findings among men and other racial groups would add to the evidence on the role of the mineral score in colorectal cancer risk.

The etiology of colorectal cancer is heavily influenced by lifestyle and dietary factors, and minerals may be promising chemopreventative measures against the disease.

Appendices

Table A.1. Sensitivity analyses for multivariable-adjusted associations[a] of the mineral score[b] with risk for incident colorectal cancer among older women; Iowa Women's Health Study, 1986-2012

	# cases	Sensitivity Analysis 1[c] (HR, 95% CI)	Sensitivity Analysis 2[d] (HR, 95% CI)
Mineral score continuous	1,744	0.99 (0.97, 0.99)	0.99 (0.97, 1.01)
Mineral score quintiles (median)			
1 (12)	286	1 (referent)	1 (referent)
2 (15)	346	1.01 (0.93, 1.23)	0.91 (0.77, 1.07)
3 (17)	367	0.97 (0.87, 0.99)	0.87 (0.73, 1.03)
4 (18)	365	0.83 (0.80, 0.86)	0.87 (0.73, 1.05)
5 (21)	380	0.78 (0.65, 0.90)	0.86 (0.73, 1.02)
P-trend		*0.002*	*0.002*

Abbreviations: HR, hazards ratio; CI, confidence interval

[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, total fiber intake, total fruit and vegetable intake, red and processed meat intake, alcohol, and dietary oxidative balance score

[b] Mineral score 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] Excluding those who died or were diagnosed with colorectal cancer during first year follow-up (see text)

[d] Censored at age 75 (see text)

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

Mineral	HR, 95% CI	
	Mineral score continuous	Mineral score upper quintile
Calcium	0.99 (0.98, 1.01)	0.75 (0.70, 1.00)
Copper	0.94 (0.87, 0.99)	0.76 (0.72, 0.98)
Iodine	0.99 (0.97, 1.02)	0.76 (0.73, 1.00)
Iron	0.98 (0.96, 0.99)	0.74 (0.67, 0.92)
Magnesium	0.99 (0.98, 1.01)	0.76 (0.75, 1.06)
Manganese	0.98 (0.96, 1.00)	0.75 (0.73, 0.98)
Phosphorus	0.99 (0.97, 1.00)	0.74 (0.72, 1.06)
Potassium	0.99 (0.97, 1.02)	0.75 (0.73, 0.98)
Selenium	0.97 (0.96, 0.99)	0.75 (0.71, 1.01)
Sodium	0.99 (0.96, 1.00)	0.74 (0.73, 0.97)
Zinc	0.98 (0.96, 1.00)	0.74 (0.72, 0.99)

Abbreviations: HR, hazards ratio; CI, confidence interval

[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, total fiber intake, total fruit and vegetable intake, red and processed meat intake, alcohol, and dietary oxidative balance score

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

Table A.3. Multivariable-adjusted associations[a] of the mineral score[b] with incident colorectal cancer, by colon site; Iowa Women's Health Study, 1986-2012

	Proximal [c] (HR, 95% CI)	Distal [d] (HR, 95% CI)
# of cases	1064	680
Mineral score continuous	0.96 (0.91, 1.01)	1.02 (0.95, 1.09)
Mineral score quintiles (median)		
1 (12)	1 (referent)	1 (referent)
2 (15)	0.89 (0.72, 1.10)	0.72 (0.55, 0.93)
3 (17)	0.98 (0.79, 1.21)	0.77 (0.59, 1.00)
4 (18)	0.85 (0.68, 1.06)	0.86 (0.65, 1.12)
5 (21)	0.82 (0.65, 1.04)	0.96 (0.71, 1.29)
P-trend	*0.001*	*0.002*

Abbreviations: HR, hazards ratio; CI, confidence interval

[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, total fiber intake, total fruit and vegetable intake, red and processed meat intake, alcohol, and dietary oxidative balance score (see text)

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

[c] Proximal = ICD-O codes 18.0-18.6, 18.8-18.9

[d] Distal = ICD-O codes 18.7, 19.9, 20.9

Table A.4. Multivariable-adjusted associations[a] of the mineral score[b] with incident colorectal cancer, according to levels of other selected risk factors; Iowa Women's Health Study, 1986-2012

		Mineral score tertiles		
Characteristics	**Strata**	**Tertile 1 HR (95% CI)**	**Tertile 2 HR (95% CI)**	**Tertile 3 HR (95% CI)**
Age, yrs	< 61	1.0 (ref)	0.82 (0.68, 0.99)	0.76 (0.62, 0.92)
	≥ 61	1.0 (ref)	0.87 (0.75, 1.01)	0.86 (0.73, 1.00)
Height, cm	< 160	1.0 (ref)	0.79 (0.66, 0.95)	0.71 (0.58, 0.87)
	≥ 160	1.0 (ref)	0.90 (0.77, 1.04)	0.90 (0.77, 1.05)
BMI, kg/m^2	< 25	1.0 (ref)	1.0 (0.82, 1.23)	0.92 (0.74, 1.13)
	25 - 30	1.0 (ref)	0.74 (0.61, 0.89)	0.75 (0.61, 0.91)
	≥ 30	1.0 (ref)	0.89 (0.70, 1.19)	0.94 (0.72, 1.21)
Waist-hip ratio	< 0.83	1.0 (ref)	0.92 (0.77, 1.11)	0.87 (0.72, 1.05)
	≥ 0.83	1.0 (ref)	0.83 (0.71, 0.96)	0.84 (0.71, 0.99)
Smoking status	Current	1.0 (ref)	0.83 (0.61, 1.14)	0.74 (0.53, 1.05)
	Former	1.0 (ref)	1.01 (0.75, 1.35)	0.80 (0.60, 1.08)
	Never	1.0 (ref)	0.80 (0.69, 0.92)	0.83 (0.72, 0.97)

		Mineral score tertiles		
Characteristics	**Strata**	**Tertile 1 HR (95% CI)**	**Tertile 2 HR (95% CI)**	**Tertile 3 HR (95% CI)**
Physical activity level	Low	1.0 (ref)	0.81 (0.69, 0.95)	0.88 (0.74, 1.04)
	Medium	1.0 (ref)	0.90 (0.72, 1.14)	0.81 (0.63, 1.04)
	High	1.0 (ref)	0.94 (0.71, 1.23)	0.86 (0.65, 1.13)
HRT use	Current	1.0 (ref)	0.72 (0.47, 1.10)	0.76 (0.50, 1.15)
	Former	1.0 (ref)	0.89 (0.70, 1.14)	0.92 (0.72, 1.19)
	Never	1.0 (ref)	0.88 (0.76, 1.01)	0.83 (0.71, 0.96)
Education	< College graduation	1.0 (ref)	0.87 (0.72, 0.98)	0.84 (0.74, 0.96)
	College Graduation or higher	1.0 (ref)	0.69 (0.47, 1.00)	0.68 (0.47, 0.98)
Family history	No	1.0 (ref)	0.82 (0.72, 0.92)	0.78 (0.69, 0.89)
	Yes	1.0 (ref)	2.05 (0.94, 4.46)	1.79 (0.80, 3.99)
Diabetes	No	1.0 (ref)	0.85 (0.75, 0.98)	0.81 (0.71, 0.92)
	Yes	1.0 (ref)	0.70 (0.43, 1.13)	0.86 (0.54, 1.38)
Total energy intake, kcal/day	< 1,716	1.0 (ref)	0.85 (0.71, 1.01)	0.79 (0.66, 0.94)
	≥ 1,716	1.0 (ref)	0.83 (0.78, 0.97)	0.80 (0.67, 0.97)

Characteristics	Strata	Mineral score tertiles Tertile 1 HR (95% CI)	Tertile 2 HR (95% CI)	Tertile 3 HR (95% CI)
Total fat intake, gm/day	< 64	1.0 (ref)	0.84 (0.69, 1.02)	0.77 (0.63, 0.92)
	≥ 64	1.0 (ref)	0.84 (0.72, 0.97)	0.84 (0.70, 1.02)
Dietary fiber intake, gm/day	< 5	1.0 (ref)	0.89 (0.76, 1.05)	0.86 (0.72, 1.02)
	≥ 5	1.0 (ref)	0.81 (0.68, 0.96)	0.79 (0.66, 0.94)
Total fruit and vegetable intake, servings/day	< 40.5	1.0 (ref)	0.85 (0.73, 1.00)	0.81 (0.68, 0.96)
	≥ 40.5	1.0 (ref)	0.86 (0.72, 1.02)	0.85 (0.71, 1.01)
Red and processed meats intake, servings/day	< 6	1.0 (ref)	0.84 (0.70, 1.02)	0.75 (0.62, 0.90)
	≥ 6	1.0 (ref)	0.84 (0.72, 0.98)	0.90 (0.75, 1.08)
Alcohol intake, gm/day	< 15	1.0 (ref)	0.84 (0.74, 0.95)	0.83 (0.73, 0.94)
	≥ 15	1.0 (ref)	1.00 (0.64, 1.55)	0.71 (0.43, 1.17)
Dietary OBS	< -0.67	1.0 (ref)	1.22 (0.80, 1.13)	1.03 (0.94, 1.09)
	≥ -0.67	1.0 (ref)	0.81 (0.71, 1.03)	0.72 (0.71, 0.95)

Abbreviations: BMI, body-mass index; HRT, hormone replacement therapy; OBS, oxidative balance score;

HR, hazards ratio; CI, confidence interval

[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, total fiber intake, total fruit and vegetable intake, red and processed meat intake, alcohol, and dietary oxidative balance score (see text)

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