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Mineral intakes and risk of incident, sporadic colorectal adenoma

By

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Master of Public Health

Epidemiology

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An abstract of
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Abstract

Mineral intakes and risk of incident, sporadic colorectal adenoma

By Chenjie Zeng

Basic science and animal experiment evidence suggests that mineral intakes may affect risk for colorectal cancer. This study was conducted to investigate whether magnesium, copper, zinc, calcium, and iron intakes, separately or combined, are associated with the risk of incident, sporadic colorectal adenomatous polyps.

Data were analyzed from a case-control study of incident, sporadic adenoma cases (n=566), colonoscopy-negative controls (n=687), and community controls (n=535) in Minneapolis-St. Paul, Minnesota between 1990 and 1994. Self-administered questionnaires were used to collect dietary and lifestyle information. A mineral score where high and low non-iron mineral exposures were assigned values of 1 and 0, respectively, while high and low iron exposures were assigned values of 0 and 1, respectively, was created. Unconditional logistic regression was used to examine whether intakes of magnesium, copper, zinc, calcium, iron, or the combined mineral score were associated with risk of adenoma; whether the association of the combined score with colorectal adenoma is modified by demographic, dietary and lifestyle factors; as well as whether the association differs according to specific adenoma characteristics.

Higher copper intake was associated with a lower risk of adenoma (cases vs. colonoscopy-negative controls: odds ratio (OR) = 0.63, 95% confidence interval (CI): 0.35, 1.16; cases vs. community controls: OR=0.54, 95% CI: 0.30, 0.97). No statistically significant associations of intakes of magnesium, zinc, calcium, or iron were found. Risk of adenoma was approximately 30% lower among those in the highest versus lowest categories of the combined mineral scores (cases vs. colonoscopy-negative controls: OR = 0.69, 95% CI: 0.41, 1.15; cases vs. community controls: OR=0.75, 95% CI: 0.46, 1.22). The results on the association between mineral scores and risk of adenoma did not substantially differ according to demographic, lifestyle, or dietary factors. The inverse association was stronger for multiple and large adenomas as well as those with moderate or severe dysplasia.

This study supports the hypothesis that higher intakes of non-iron mineral combined with lower iron intake may be associated with a lower risk of incident, sporadic colorectal adenomas polyps, especially for adenomas with advanced characteristics.

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CHAPTER 1. INTRODUCTION AND BACKGROUND

Introduction

Colorectal cancer, the third most common incident cancer and the second most common cause of cancer death in the U.S (1), is a disease highly associated with environmental factors. Previous studies found “westernized” dietary pattern is one of the most important risk factors for colorectal cancers (2).

There is increasing evidence suggesting that oxidative stress is an important etiologic factor in colorectal carcinogenesis. Magnesium, copper, zinc and calcium play a role in reducing oxidative stress (3-6), which may affect colorectal cancer risk. Iron has been proposed a risk factor in colorectal carcinogenesis due to its high oxidative potential (7). There have been few epidemiological studies on intakes of magnesium, copper, and zinc and colorectal cancer risk, and the finding from them have not been consistent. There is substantial epidemiologic evidence that higher calcium intake reduces risk for colorectal cancer (8-11). Epidemiologic studies on total iron intake and colorectal cancer risk have been inconsistent.

In most patients, colorectal cancer develops from adenoma over years. The data on the association of magnesium, zinc, copper, and iron with adenoma risk have been sparse and inconsistent (12), likely due to the close interrelations between the minerals. There are both antagonisms and synergisms among these minerals. For example, magnesium shares the same ion channels with calcium, which may result in suppressing the absorption and transportation of calcium (13). On the other hand, there is a synergism between calcium, and magnesium since both are required in the maintenance and structure of osseous tissue (13). Similar patterns of antagonisms and synergisms of

copper and zinc are also observed (13). Because of the similar functions of these non-iron minerals (magnesium, copper, zinc, and calcium) as antioxidant-related micronutrients and their close interactions, we hypothesize that a combined mineral score of high non-iron minerals intakes and low iron intakes will represent the overall exposure of minerals as antioxidants. It is also biologically plausible that there are agents or conditions that can modify the association of minerals and colorectal adenomas risk.

Chapter 2 examined the association of intakes of magnesium, copper, zinc, calcium, and iron with risk for colorectal adenomas separately and combined in a case-control study. The study questions in this study are: 1) are higher intakes of non-iron minerals and lower intake of iron separately, or combined, associated with lower risk of adenomas; 2) is the association of a mineral score representing higher intakes of non-iron minerals and lower intake of iron with adenoma risk modified by inflammation status, obesity, sex, age and dietary factors; and 3) does the association differ according to different adenoma characteristics.

Background

Descriptive epidemiology of colorectal cancer

Colorectal cancer (CRC) is the second leading cause of cancer deaths in the United States. Approximately 102,900 new colon cancer cases and new 39,670 rectum cancer cases were anticipated in 2010 in the United States (1). The colorectal cancer incidence rate decreased slightly during the past 20 years. Colon cancers affect males and females equally, while rectal cancers occur in males more frequently than females (14). The incidence rate increases as age increases. Approximately 90% of colorectal cancer cases occur in persons of age 50 or older (15). The mortality of colorectal cancer has been

decreasing in the United States, particularly in females, with steeper decline in the past decade (14), due to the increased awareness of screening and advanced medical treatments.

International studies have observed that the incidence of colorectal cancers varied significantly across countries. The highest incidence and mortality rates are seen in the "westernized " countries of North American, Europe and Oceania, and the lowest rates are in Asia, South America and Africa (16). In contrast to the trend in the U.S, colorectal cancer incidence worldwide increased significantly, largely confined to the increase in economically transitioning countries including Eastern European countries (17), Asian countries and some South American countries. Substantial variation in colorectal cancer incidence trends across countries was observed. For example, large increase was found in Japan, Kuwait and Israel, while countries, like France and German, the incidence rate remain stable or slightly increased (16, 17).

Migration studies found that increased risk of colorectal cancer was associated with immigration to westernized countries. As an example, Japanese, Chinese, Korean who migrated to the United States had a higher incidence rate of colorectal cancers than their counterparts in their home countries. Their descendents tended to acquire the incidence rates in the United States (18).

Colorectal carcinogenesis

Colorectal cancer refers to three neoplastic diseases, including the proximal colon cancer, the distal colon cancer and the rectum cancer. Most colorectal cancers, at least two third and perhaps as much as ninety percent, arise from adenomatous polyps. The likelihood of

malignancy in an adenomatous polyp and the likelihood of transforming into a cancer depend on its size, histological type, and degree of dysplasia. Adenomas progress from small (1-5 mm) to medium (6-9 mm) to large (10+ mm) size. The risk of developing into cancer increases as the size increases. There are three histological subtypes of adenomas: tubular, villous, and tubulovillous (19). The most life-threatening adenomas are villous adenomas, which are usually large and sessile. The least dangerous type is tubular. It is estimated that approximately 50% of large villous adenomas transform into cancer[6, 7].

Several molecular pathways have been identified in the transformation of normal colorectal cells to cancer cells. The most important pathway in the adenoma-carcinomas sequence is APC-β-catenin-Tcf-MYC pathway. Colorectal malignancy is often initiated by a mutation in APC gene which may lead to the familial adenomatous polyposis syndrome (FAP), characterized by the development of multiple colorectal adenomas. APC gene mutations increase the concentrations of β-catenin, which adheres to the T-cell factor 4 (Tcf4), and mediates transcription of certain genes including the oncogene c-myc. Other genetic or epigenetic alterations, such as DNA hypomethylation and mutations of the K-ras and p53 genes are also needed to transform the mutated cells to cancerous cells. The second pathway is the “Mismatch Repair (MMR) Pathway”, which accounts for hereditary non-polyposis colon cancer (HNPCC) genetic syndromes. Several mismatch repair genes have been identified: hMLH1, hMSH2, hPMS1, hPMS2 and hMSH6, among which, hMLH1 and hMSH6 are the most common genes found in HNPCC cases (20). Another pathway is the serrated adenoma pathway, includes BRAF or K-ras mutations combined with extensive DNA methylation during early stages of cancer development, and leads to sporadic colorectal cancers (21).

Analytical epidemiology of colorectal cancer

As previously stated, the strongest known risk factors for colorectal cancer that have been identified so far are FAP and HNPCC, as well as extensive ulcerative colitis(15). These conditions account for 5 to 10% of the colorectal cancer cases. Of the remaining cases, 30% have a family history of this disease, which confers a 2- to 3 folds increase in risk. About 65% of the cases are incident and sporadic (15). Both international studies and migration studies suggested that western lifestyle is an important risk factor for incident, sporadic colorectal cancer.

Based on previous studies and data on lifestyle and diet, World Cancer Research Fund and American Institute for Cancer Research reported that physical activity of all levels decreases the colorectal cancer risk wile high intakes of red and processed meats, alcoholic drinks in males and high body weight cause colorectal cancers (22). These factors are reviewed in the next section as well as other probable risk factors.

Physical activity and body mass index

There is convincing evidence that physical activity is inversely associated with colon cancer risk. There are several biological mechanisms that may support this association: decreasing insulin resistance; decreasing inflammation; decreasing intestinal transit time, increasing vitamin D levels; reducing body fatness; reducing hyperinsulinemia and modulating immune function (23, 24). A meta-analysis of 52 studies found a 25% lower risk of colon cancer were associated with the highest level of physical activities, relative to the lowest. The inverse associations did not differ over time (23). Another recent meta-analysis that investigated the relation of physical activity with adenomas found a

significant inverse association with an overall RR of 0.84 (95% CI: 0.77, 0.92). Unlike colon cancer or colon adenoma, the association of physical activity and rectal cancer has been inconsistent.

Higher body max idex (BMI) is a well-established risk factor for colorectal cancers. A recent systematic review that analyzed 29 datasets including 67,361 incident cases concluded that increasing BMI (5 kg/m^2) was associated with a modest increased risk and the association was more strong in men than in women (for colon cancer in men: RR=1.24, 95% CI: 1.20,1.28; for colon cancer in women: RR=1.09, 95% CI: 1.04, 1.152; for rectal cancer in men: RR=1.09, 95% CI: 1.05, 1.14; for rectal cancer in women: RR=1.05, 95% CI 0.99, 1.12) (25). These findings were consistent with the other meta-analyses with different analysis methods (26-28).

Alcohol and smoke

Alcohol consumption is a well-recognized risk factor, especially for men. A recent meta-analysis of 27 cohort and 34 case-control studies reported a sharp dose-response relationship between alcohol and colorectal cancer risk, a statistically significant 7% increased colorectal cancer risk for 10 g/day of alcohol intake. Compared with nondrinkers or occasional alcohol drinkers, moderate drinking (1–4 drinks/day) was associated with a 21% and heavy drinking (≥4 drinks/day) with a 52% increased risk for colorectal cancer (29). There are several hypotheses about a possible increased risk with alcohol consumption, including producing acetaldehyde through oxidation and initiating irregular DNA methylation.

The relation of smoking and colorectal cancer has been controversial. Most of the early studies suggested no association whereas recent studies with follow-up after 1970 in general supported a positive association. It has been suggested that there may be a lag period of 30-40 years between this exposure and outcome (30). There are three meta-analysis of the association between smoking and colorectal cancer risk. Chen et al. reported a positive association with the meta-analysis of 14 case control studies in China(31); Botteri et al. found a significant association between smoking and colorectal adenomas (32); Liang et al. found that smokers had a higher risk of colorectal cancer incidence and mortality and there was a significant positive dose-response relationship between smoking and colorectal cancer risk (30). The possible mechanism is that the inhaled smoke contains carcinogens that may reach colorectal tissues through the digestive tract and circulatory system (33, 34).

Nonsteroidal anti-inflammatory drugs

There is growing evidence that nonsteroidal anti-inflammatory drugs (NSAIDs) reduce risk for colorectal cancer. Two recent systematic reviews reported that NSAIDs reduced colorectal cancer incidence or adenoma incidence. Rostom et al. found that non-aspirin NSAID reduced colorectal adenoma risk (cohort studies: RR=0.64 95% CI: 0.48, 0.85; case-control studies: RR=0.54 95% CI: 0.4, 0.74) and colorectal cancer risk (cohort studies: RR=0.61 95% CI: 0.48, 0.77; case-control studies RR= 0.70 95% CI: 0.63, 0.78) (35). Dube et al. reported that regular use of aspirin reduced the incidence of colonic adenomas in randomized trials (RR=0.82, 95% CI: 0.7, 0.95) and in cohort studies (RR=0.71, 95% CI: 0.61, 0.85). The protective effect was more evident when aspirin was used at a high dose and for periods longer than 10 years (36). The proposed mechanism is

that NSAIDs are able to block the production of COX-2, which catalyzes a reaction that produces prostaglandin E2 that is important in colorectal cancer development. However, NSAIDs are also associated with important cardiovascular events and gastrointestinal harms (35, 36). Further evaluation on the chemoprevention use of NSAIDs is warranted.

Hormone replacement therapy

Investigations on hormone replacement therapy (HRT) and colorectal cancer in women are not consistent. A meta-analysis of 18 observational studies concluded that the current use of hormone therapy was associated with a reduced risk of colorectal cancer (37). In the Women's Health Initiative clinical trial study, risk of colorectal cancer was not reduced in association with estrogen use (38) but significantly reduced in the association with estrogen and progestin therapy (39). It is proposed that HRT may reduce the DNA methylation levels of estrogen receptor and related genes and thus reduce the risk of colon cancer (40, 41).

Red meat and processed meat

Red meat and processed meat is positively associated with incident, sporadic colorectal cancer risk. Three recent meta-analyses showed intake of red or processed meat is associated with a modest, but significant higher risk of colorectal cancer. Alexander et al estimated that a significant dose-response relationship of processed meat. For each 30-gram increment of processed meat, the RR for colorectal cancer was 1.10 (95% CI: 1.05-1.15) based on nine prospective studies (42). Larsson et al. found that individuals with highest intakes of red meat or processed meat had a 28% and 20% respectively, increased risk of colorectal cancer, compared to those with lowest intakes through a meta-analysis

with 19 prospective studies and approximating 8,000 cases (43). Norat et al. also observed a significant dose-response relationship for red meat intake or processed meat intake. The estimated RR for colorectal cancer were 1.24 (95% CI: 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 (44). Several mechanisms may explain the positive relationship, including mutagenic heterocyclic amines generated during the high temperature cooking of meat (45), the high saturated fat content of red and processed meat which increases the risk and also the high heme-iron which is consider pro-oxidant and thus increases the risk (46).

Fruit and vegetables

The epidemiologic evidence on the inverse association between fruit and vegetable intake and colorectal cancer risk was not consistent. The proposed mechanisms include antioxidant activity, regulation of immunologic response, alteration of hormone metabolism, and antiproliferative activities (47). Data from a recent meta-analysis of fourteen cohort studies including 5, 838 cases suggested a very small inverse and non-significant association between intake of total fruits and vegetables and cancer risk (48). In the polyp prevention trial, a low-fat, high-fiber, increased fruit and vegetables diet was found no effect on recurrence of colorectal adenomas after eight years of randomization (49).

Folate

There is much evidence suggesting folate may reduce the colorectal cancer risk. Folate is a water-soluble vitamin B that is essential for DNA repair, synthesis, and methylation. A

recent meta-analysis of 13 cohort studies including 725,134 participants and 5,720 incident colon cancers reported that folate intake was inversely associated with risk for colon cancer (highest categories of intake vs. lowest: RR = 0.87, 95% CI: 0.78, 0.98) (50). Another meta-analysis of 7 cohort studies reported a similar result (highest categories of intake vs. lowest: RR = 0.75, 95% CI: 0.64,0.89) (51) .

Vitamin D

There is substantial evidence that vitamin D reduces colorectal cancer risk. A recent meta-analysis of 42 epidemiological studies found a statistically significant inverse dose response association between dietary vitamin D and colorectal cancer (for an increase of 100 IU/day, RR=0.94, 95% CI: 0.93, 0.98). The proposed mechanisms include that vitamin D modulates more than 200 genes involved in colorectal cancer genesis (52) , regulates differentiation and apoptosis, promotes bile acid degradation and xenobiotic metabolism, and regulates immune function (53).

Minerals and colorectal cancers

Several studies have suggested that mineral supplement intake may be associated with a lower risk of colorectal cancer (54-56). Several biological mechanisms may explain the association, including reducing oxidative stress, binding bile acid, regulating immunological response, maintaining genome stability, and preventing DNA damage (57).

Magnesium

Magnesium is the second most abundant intracellular cation in human body, which is needed for more than three hundred physiological activities. About 90% of the

magnesium in the body is bound and the rest is free. The intracellular magnesium is mainly bound to nucleic acids, ATP, negatively charged phospholipids and proteins (58). Magnesium plays an essential role in energy metabolic processes, in protein synthesis, membrane integrity, nervous tissue conduction, neuromuscular excitability, muscle contraction, hormone secretion, and in intermediary metabolism (59). There is no evidence on whether magnesium homeostasis is controlled by hormones (58). According to the data from the National Health and Nutrition Examination Survey 2005–2006, approximately 60% of the U.S. adults failed to consume adequate amount of magnesium (60). Low magnesium intake has been linked to numerous chronic inflammatory conditions (61-64).

There is growing evidence showing that low magnesium intake is associated with an increased risk of colorectal cancer. Animal studies found that administration with supplemental magnesium reduced the number of colon cancers and the size of cryptal cells in animals with induced colon cancers (65). The proposed mechanisms of magnesium against colorectal cancer include the inhibitory role in c-myc oncogene expression in the colon cancer cells (65), and the potential ability of binding bile acids on colonic epithelial cells (66), as well as the modulating role in insulin homeostasis which is associated with colorectal cancer risk (67). A majority of observational studies on the association of magnesium intake and colorectal cancer risk supported the protective effect of magnesium (68-70). However, other studies found no inverse associations (71-74). A recent study suggested that the ratio of calcium to magnesium (Ca:Mg) intake may be more important in the carcinogenesis of colorectal cancers. The inverse association of magnesium appeared only among those with a low Ca:Mg intake (12). There may be

effect modification by type 2 diabetes status in the association between magnesium intake and risk of colorectal cancers according to a cohort study in Netherland(71).

Copper

Copper is a trace element found in a variety of cells and tissues. It can bind to proteins and become an integral part of many important enzymes involved in a number of vital biological processes. Copper can be both antioxidant and pro-oxidant. There are two forms of copper in the human body, an oxidized, cupric (Cu^{2+}), or reduced, cuprous (Cu^{+}), state. The characteristic of easy release and absorption of one electron makes copper particularly useful in oxidation-reduction reactions and free radical scavenging (75). Copper is required for structural and catalytic properties of important enzymes that are involved in oxidation processes, for example, cytochrome c oxidase, tyrosinase, lysyl oxidase, and Cu-zinc superoxidase dismutase (Cu, Zn-SOD) (76-78). Copper is able to combine and react with molecular oxygen and/or oxygen-derived reactive species (79). A deficiency in dietary copper may increase cellular susceptibility to oxidative damage which may lead to cancers. Because of these characteristics, copper has been investigated as an anticancer agent. For example, copper complexes of thiosemicarbazonates have shown promising anticancer activities (80). On the other hand, chronic copper overload may also lead to oxidative stress conditions. However, copper overload is quite rare, since the amount of copper in water and food is limited and most humans are able to control the excessive amount of copper in the body by either reducing absorption or increasing excretion (5).

Several animal studies show that inadequate dietary copper increased the risk of chemically-induced colon cancers in mice and rats (81). However, epidemiologic studies that investigated copper as a related factor of colorectal cancers were sparse and inconsistent. A case control study investigating dietary patterns and colon cancer risk in Hong Kong suggested that copper was a independent protective agent against colon cancer (82). A case control study in a Portuguese population observed a statistically significant 60% decrease in the risk of colorectal cancer among those in the highest quartile of copper intake compared to those in the lowest quartile (83). Another case study in France reported that high copper intake was associated with an increase risk of colorectal cancer (OR=2.4, 95% CI: 1.3-4.6) (84).

Zinc

Zinc has been known to be a vital trace element in the body and plays an important role in cell proliferation and may retard oxidative processes. Zinc is required for the activities of over 300 enzymes and participates in many enzymatic and metabolic functions in the body. Over two thousand transcription factors involved in gene expression require zinc for their integrity and their ability of binding to DNA (85). Zinc functions as an antioxidant in the human body. Zinc is an important component of Cu, Zn-SOD (76-78). Zinc is an inhibitor of NADPH oxidases which catalyze the production of superoxide radical from oxygen, and thus prevents generation of strong oxidants.

The role of zinc in carcinogenesis has been well studied in cell biology and animal models. The levels of zinc have been shown to be lower in cancer cells compared to normal cells. Zinc may also be involved in the growth regulation of human colorectal

cells (86). Animal studies suggested that low zinc intake might increase the risk of colorectal cancer (87, 88).

There are few epidemiologic studies assessing zinc intake and colorectal cancer risk. In Iowa Women's Health Study, an inverse association between high zinc intake and risk of colorectal cancer (Relative Risk (RR) = 0.22, 95% CI: 0.07, 0.67) was observed among postmenopausal female drinkers, though no significant association was found in all the participants. Another cohort study in Sweden reported no association between zinc intake and colorectal cancer risk (RR=0.84, 95% CI: 0.64, 1.09).

Calcium

Calcium is an element that participates in numerous physiological activities in the body. The functions of calcium include intracellular signaling and cell proliferation and differentiation. Calcium homeostasis is controlled by three hormones: vitamin D, parathyroid hormon, and calcitonin (89). Animal studies have suggested that calcium may be involved in the etiology of colon cancer (90). Proposed mechanisms of calcium against colorectal cancer include binding bile acids and fatty acids, direct effects on cell cycle regulation, modulation of the APC colon carcinogenesis pathway through mediating E-cadherin and β-catenin expression via the calcium-sensing receptors (90).

There is substantial evidence that calcium may have a protective effect against colorectal cancer. A recent meta-analysis of 60 observational studies including 26,335 cases reported a significant inverse association between dietary and supplemental calcium intakes and colorectal cancer risk (RR=0.77, 95% CI: 0.71, 0.81) (91). These findings are consistent with another meta-analysis in 2004 which included 10 cohort studies and

reported a summary relative risk of 0.78 (95% CI: 0.69, 0.88; P_{trend}<.001) (11). A meta-analysis of randomized controlled trials found that supplemental calcium was effective for the prevention of adenoma recurrence. However, the researchers did not find a significant protective effective on colorectal cancer (92).

Iron

Iron is a trace element involving in numerous biological processes such as oxygen transport and DNA synthesis as well as cell cycle progression. There are two forms of dietary iron, heme iron from red meat and non-heme iron from plants and dairy products. The relationship between heme iron and colorectal cancer has been studied in the purpose of explaining the increased risk of colorectal cancer associated with red meat intake. The hypothesized mechanism is that heme iron is pro-oxidant and damages DNA by free radicals generated by the Fenton reaction (93). Fifteen epidemiologic studies, including five cohort studies, seven case control studies, and two ecological studies examined the association between iron intakes and colorectal cancer risk. Twelve of these studies were in favor of a positive association between dietary iron and colorectal cancer (46, 84, 94-102), while the rest studies observed no significant association between dietary iron intake and colorectal cancer risk (103).

A recent meta-analysis of heme iron and colorectal cancers risk including data on 566,607 individuals and 4,734 cases of colon cancer in cohort studies concluded that the RR of colon cancer for all the cohort studies was 1.18 (95% CI: 1.06–1.32) for subjects in the highest category of heme iron intake compared with those in the lowest category. This study suggested a consistent positive association between high iron intake and

colorectal cancer risk (104). The study also indicated that it may be necessary to adjust for calcium intake when evaluating the association between iron intake and risk of colorectal cancer since calcium is able to inhibit the heme iron induced cytotoxicity (105).

CHAPTER 2. MINERAL INTAKES AND RISK OF INCIDENT, SPRORADIC COLORECTAL ADENOMA

Abstract

Basic science and animal experiment evidence suggests that mineral intakes may affect risk for colorectal cancer. This study was conducted to investigate whether magnesium, copper, zinc, calcium, and iron intakes, separately or combined, are associated with the risk of incident, sporadic colorectal adenomatous polyps.

Data were analyzed from a case-control study of incident, sporadic adenoma cases (n=566), colonoscopy-negative controls (n=687), and community controls (n=535) in Minneapolis-St. Paul, Minnesota between 1990 and 1994. Self-administered questionnaires were used to collect dietary and lifestyle information. A mineral score where high and low non-iron mineral exposures were assigned values of 1 and 0, respectively, while high and low iron exposures were assigned values of 0 and 1, respectively, was created. Unconditional logistic regression was used to examine whether intakes of magnesium, copper, zinc, calcium, iron, or the combined mineral score were associated with risk of adenoma; whether the association of the combined score with colorectal adenoma is modified by demographic, dietary and lifestyle factors; as well as whether the association differs according to specific adenoma characteristics.

Higher copper intake was associated with a lower risk of adenoma (cases vs. colonoscopy-negative controls: odds ratio (OR) = 0.63, 95% confidence interval (CI): 0.35, 1.16; cases vs. community controls: OR=0.54, 95% CI: 0.30, 0.97). No statistically significant associations of intakes of magnesium, zinc, calcium, or iron were found. Risk of adenoma was approximately 30% lower among those in the highest versus lowest categories of the combined mineral scores (cases vs. colonoscopy-negative controls: OR = 0.69, 95% CI: 0.41, 1.15; cases vs. community controls: OR=0.75, 95% CI: 0.46, 1.22). The results on the association between mineral scores and risk of adenoma did not substantially differ according to demographic, lifestyle, or dietary factors. The inverse association was stronger for multiple and large adenomas as well as those with moderate or severe dysplasia.

This study supports the hypothesis that higher intakes of non-iron mineral combined with lower iron intake may be associated with a lower risk of incident, sporadic colorectal adenomas polyps, especially for adenomas with advanced characteristics.

Introduction

Colorectal cancer, the third most common incident cancer and the second most common cause of cancer death in the U.S (1), is a disease highly associated with environmental factors. Previous studies found that the "westernized" dietary pattern is one of the most important risk factors for colorectal cancers (2).

Magnesium, copper, zinc, and calcium play roles in reducing oxidative stress. Magnesium is an important cofactor in maintaining genome stability and regulating cell cycles (106). It is hypothesized magnesium deficiency may decrease the integrity of the membrane and thus increase the vulnerability to oxidative stress (106). Low magnesium intake has been linked to numerous chronic inflammatory conditions (61-64). Animal studies found that supplemental magnesium reduced the number of colon cancers and the size of cryptal cells in animals with induced colon cancers (65). Copper and zinc are trace elements that are required for the structural and catalytic properties of important enzymes involved in oxidation processes, such as Cu-zinc superoxidase dismutase (Cu, Zn-SOD) (76-78). A deficiency in dietary copper and zinc may increase cellular susceptibility to oxidative damage which may lead to cancers (5). Zinc also plays an important role in cell proliferation (85). Animal studies suggested that low zinc intake might increase the risk of colorectal cancer (87, 88). Calcium is an element that is essential for intracellular signaling and cell proliferation and differentiation. It also plays a role in modulating oxidative stress (107). High calcium intake reduces colon cancer tumorgenesis in animal studies (52). Iron is a trace element involving in numerous biological processes such as oxygen transport and DNA synthesis as well as cell cycle progression (6). The carcinogenic potential of iron in colorectal cancer remains unclear (7). It is thought that

iron mediates the generation of reactive oxygen through the Fenton reaction, which leads to lipid peroxidation (108), which may lead to DNA damage and later neoplasia. Administration of iron increased colon cancer cell growth. (109).

There have been few observational studies on associations of magnesium, copper, and zinc intakes with colorectal cancer risk, and the results have been inconsistent (68-74, 82, 84, 96, 98). There is growing epidemiologic evidence that higher calcium intake reduces colorectal cancer risk (8-11). Epidemiologic studies on total iron intake and colorectal cancer risk have been inconsistent (101, 103, 110-112). However, via a recent meta-analysis of 5 cohort studies on heme iron intake and risk of colorectal cancer, a positive association of heme iron intake with colorectal cancer was found (summary relative risk (RR): 1.18, 95% CI: 1.06, 1.32) (104).

In most patients, colorectal cancer develops from adenoma over years. The data on the association of magnesium, zinc, copper, and iron with adenoma risk have been sparse and inconsistent (12) , likely due to the close interrelation between minerals. There are both antagonisms and synergisms among these minerals, for example, magnesium and calcium may suppress the absorption and transportation of each other. On the other hand, there is a synergism between calcium, and magnesium since they are both requirement in the maintenance and structure of osseous tissue (13). Similar patterns of antagonisms and synergisms are also observed in copper and zinc, as well as copper and iron (13). Because of the similar functions of these non-iron minerals (magnesium, copper, zinc, and calcium) as antioxidant-related micronutrients and their close interactions which may synergistically protect against colorectal carcinogenesis by influencing bile-acid metabolism and reducing oxidative stress, we created a combined mineral score of high

non-iron minerals intakes and low iron intakes to represent the overall mineral exposure. It is also biologically plausible that there are agents or conditions that can modify the association of minerals and colorectal adenomas risk. We hypothesized that 1) higher intakes of magnesium, copper, zinc or calcium are associated with a lower risk of adenomas and 2) higher mineral scores are associated with a lower risk of adenomas. To our knowledge, this is the first study to investigate a combined mineral score composed of magnesium, copper, zinc, calcium, and iron intakes and risk of colorectal adenoma. We used data from a colonoscopy-based, case-control study of incident, sporadic colorectal adenomas to investigate the association between minerals exposure and adenoma risk.

Materials and methods

Case-control study

The Cancer Prevention Research Unit study (CPRU) was a case-control study conducted between 1991 and 1994 as a part of the Minnesota Cancer Prevention Research Unit, an NCI-funded program project that combined several units within the University of Minnesota and Digestive Healthcare, PA (DH), a large multi-clinic private gastroenterology practice. The study protocol was described in detail elsewhere (113, 114). Briefly, participants in this case-control study were recruited from patients with no prior history of colorectal neoplasms who were scheduled to undergo outpatient, elective colonoscopy in any of 10 hospitals in the Minneapolis metropolitan area. Eligibility included aged 30–74 years, English speaking, willing to participate and able to understand informed consent, free of known genetic syndromes associated with predisposition to colonic neoplasia (e.g., familial polyposis coli or Gardner's syndrome), and no history of ulcerative colitis, Crohn's disease, colorectal adenomas, or cancer (except non-melanoma skin cancer). Of the 3,126 colonoscopy patients identified, 2,771 (89%) were eligible on initial screening, and of 71 these, 1,890 (68%) agreed to participate and signed consent. Of the 1,886 (99%) participants who met final eligibility criteria, 574 (30%) had a colorectal adenoma, 219 (12%) had a hyperplastic polyp but no adenoma, and 707 (37%) were free of any polyps of any type.

Data Collection

Before undergoing colonoscopy, all patients completed mailed questionnaires regarding demographic characteristics, personal medical history, and reproductive history (Women only), family history of polyps or colon cancer, anthropometrics, diet via a semi-

quantitative Willett 153-item Food Frequency Questionnaire, lifestyle, alcohol and tobacco use, usual physical activity, and reasons for colonoscopy. Preparation for colonoscopy included a 12-hour fast and bowel cleansing with polyethylene glycol. At the clinic visit, the signed consent form and completed questionnaires were collected. The colonoscopy findings were recorded on standardized forms to record colon site and *in vivo* size and shape of any polyps. Upon removal, polyps were examined histologically by an index study pathologist using diagnostic criteria established for the National Polyp Study. Only participants with a complete colonoscopy reaching the cecum were eligible. The presence or absence of pathology was determined, and based on colonoscopy and pathology findings, participants were assigned to one of the following three groups: (a) an adenomatous polyp group (defined as either adenomatous or mixed pathology); (b) a hyperplastic polyp-only group; and (c) a colonoscopy-negative control group. The hyperplastic polyp-only group was excluded from our analysis. A community control group was also recruited through the 1991 Minnesota State Drivers License Registry. Community controls were frequency matched to cases on age (using 5-year intervals), sex, and zip code (n = 247). Eligibility criteria for the community controls were identical to those for colonoscopy-negative controls. However, the presence/absence of adenomas in the community controls was unknown. The participation rate for the community controls was 65%.

The study was approved by the Institutional Review Boards of the University of Minnesota and each DH colonoscopy site. Informed consent was obtained from each participant.

Statistical Analysis

Standard techniques for case-control studies were used. The case and control groups were evaluated for comparability with respect to important covariates, including demographics, lifestyle, and other risk factors, using the Fisher's exact test for categorical variables and the ANOVA test for continuous variables.

A mineral score variable was created. Since the dataset did not include information on manganese, this mineral was excluded from our analysis. The total dietary plus supplemental intakes of magnesium, copper, zinc, calcium and iron were dichotomized based on the sex-specific median values in the community controls. For magnesium, copper, zinc, and calcium, 1 point was assigned for each high (above the median) exposure, and 0 points for each low (below the median) exposure. For iron, 0 point was assigned for high (above the median) exposure, and 1 point for low (below the median) exposure. The mineral score ranged from 0 to 5 in this study. We categorized the score into three categories: 1): score $\leq$1; 2): score $\leq$3 and 3): score>3. A questionnaire derived oxidative balance score (OBS) was also calculated as previously reported (115-117). Briefly, continuous variables reflecting pro-oxidant (saturated fat intake), and antioxidant (total tocopherol, carotenoid, vitamin C, lycopene, lutein/zeaxanthin, intake) exposures were divided into high and low categories based on the median value among community controls. Participants with low (below median) exposure to a particular pro-oxidant were assigned 1 point, whereas those with high (above median) exposure to the same pro-oxidant were assigned 0 points. For antioxidant exposure, 1 point was assigned for each high-level (above median) exposure, and 0 points for each low-level (below median) exposure. For dichotomous variables ("yes" vs. "no"), 1 point was assigned for each

antioxidant exposure (regular use of nonsteroidal anti-inflammatory drugs (NSAIDs), regular use of aspirin, supplementation with selenium, and never smoker). Then the points assigned for each individual component of OBS were summed to calculate the overall score. The OBS ranged from 0 to 10 in this study with a median value of 5 in the community controls.

Unconditional logistic regression was used to estimate the association of intakes of each mineral and the mineral score with risk of incident, sporadic colorectal adenoma. Age, sex, and hormone replacement therapy in women, education, regular use of NSAIDs and/or aspirin, family history of CRC in a first degree relative, physical activity, smoking status (current, ever, or never), BMI, total energy intake, total intakes of folate, retinol, vitamin D, fat, fiber, alcohol, red and processed meat, fruits and vegetables were considered as established or suspected confounding variables. Several techniques were used to assess confounding factors: 1) biological plausibility; 2) whether the variable of interest was associated with the outcome and exposure; and 3) whether the logistic regression coefficient of the exposure variable substantially changed (by >10%) after adding the potential confounding variable in the model. Final covariates included in multivariate-adjusted models involving the colonoscopy-negative controls were age, sex, hormone replacement therapy use (only in women), family history of colorectal cancer in a first-degree relative, total energy intake, regular use of NSAIDs or aspirin, MET (metabolic equivalent task) physical activity hours, total folate intake, total retinol intake, red meat and processed meat intake, fruits and vegetables intake, alcohol intake and smoking status. Final covariates included in multivariate-adjusted models involving for the community controls were age, sex, hormone replacement therapy use (only in

women), family history of colorectal cancer in a first-degree relative, total energy intake, regular use of NSAID or aspirin, red meat and processed meat intake, fruits and vegetables intake, dietary and supplemental vitamin C intake, alcohol intake, and smoking status. The odds ratio (OR) was the measure of association. Both crude and multivariate-adjusted ORs were calculated. For each OR, a 95% confidence interval (95% CI) was calculated. A test for trend was calculated based on the median of each quartile of mineral intake which were included in the models as continuous variables. We also examined associations stratified by age, sex, family history of colorectal cancer in a first degree relative, regular use (≥ once a week) of NSAIDs or aspirin, obesity, oxidative balance score (OBS), and total fat intake. Cut points for continuous variables investigated as potential effect modifiers were calculated based on the values of sex-specific medians in the community controls. To compare stratum-specific ORs, we included the interaction terms in the model, and tested the significance of the estimates with the log-likelihood ratio test. In addition, we investigated the associations between the mineral score and adenomas according to adenoma characteristics by classifying adenoma cases into subgroups based on multiplicity, size, location, and pathological subtype. All statistical tests were two-sided, and P-values < 0.05 were considered to be statistically significant. All statistical analyses were conducted using SAS version 9.2 software (SAS Institute, Inc., Cary, NC).

Results

Selected characteristics of cases, colonoscopy-negative controls and community controls are shown in Table 1. Compared to the colonoscopy-negative controls, cases were more likely to be older, male, and smoke and less likely to have a family history of colorectal cancer in a first degree relative. Compared to the community controls, cases were more likely to be male, smoke, have a family history of colorectal cancer in a first degree relative, and have a lower OBS.

None of the mean intakes of magnesium, zinc, iron and calcium differed substantially between cases and either sets of controls. The mean intake of copper among the cases was statistically significantly slightly lower than among the colonoscopy-negative controls, but there was no difference between the cases and the community controls. The mean mineral scores were similar across the three study groups.

Among the cases, 31% had at least one adenoma located in the right colon, 32% had multiple adenomas, 32% had an adenoma that was ≥ 1 cm in diameter, and 51% had adenomas with moderate or severe dysplasia. The largest or most advanced adenoma had villous or tubulovillous histology in 30% of all cases (data not shown).

Both the crude associations and multivariate-adjusted associations of total intakes of magnesium, copper, zinc, iron, and calcium, and of the combined mineral score with risk of incident, sporadic colorectal adenomas are shown in Table 2. In the colonoscopy-negative control group comparisons, a higher mineral score was inversely associated with colorectal adenomas (mineral score >3 vs. <2 OR=0.69, 95% CI: 0.41-1.15. A similar association was found in the analysis with the community control group (mineral score

>3 vs <2: OR=0.75, 95% CI: 0.46-1.12). In the comparisons with the community control group, there was a statistically significant 46% lower risk of colorectal adenomas for those in highest quartile of total copper intake (OR=0.54, 95% CI: 0.30-0.97), relative to those in the lowest quartile. In the comparison with the colonoscopy-negative controls, there was also a 39% lower risk of colorectal adenomas for those in highest quartile of the total copper intake, relative to those in the lowest quartile (OR=0.63, 95% CI: 0.35-1.16). For those in highest quartile of magnesium intake, risk for colorectal adenoma was lower but the associations were not significant (comparison with the colonoscopy-negative controls: OR=0.86, 95% CI: 0.44-1.68, comparison with the community controls: OR=0.61, 95% CI: 0.32-1.17). Intakes of zinc, calcium, and iron were not associated with risk of colorectal adenoma.

The multivariate-adjusted associations between the mineral score and incident, sporadic colorectal adenomas stratified by demographic, lifestyle, family history and dietary factors are shown in Table 3 and Table 4, respectively. Overall, no significant effect modification by demographic, lifestyle factors or family history was found. However, there was a suggestion of a stronger inverse association of the mineral scores with colorectal adenoma among those who regularly took NSAIDs or aspirin. In the comparisons with the community controls, higher mineral score was associated with a 52% lower risk of adenoma among those who also had a low intake of total fat (P_{trend}=0.05), while among those who had a high total fat intake, no association was observed. A similar pattern was also observed in the comparison with the colonoscopy-negative control group. In the comparison with the colonoscopy-negative controls, the odds ratio for the comparison of the highest versus lowest tertile of mineral score was

0.46 (95% CI: 0.21, 0.99) among those who had a low OBS score. No such an association was found among those with a high OBS.

The multivariate-adjusted associations of the mineral score with risk of adenomas according to various adenoma subtypes are shown in Table 5. In the comparison with the colonoscopy-negative controls, there was a statistically significant lower risk of multiple adenomas for those in the highest mineral score category (OR=0.35, 95% CI: 0.16, 78, P_{trend}=0.01), while no significant inverse association trend was found for single adenoma. The inverse association of the mineral score with risk of adenomas were also more pronounced (highest mineral score tertile vs. lowest mineral score tertile OR=0.53, 95% CI: 0.23, 1.11, P_{trend}=0.09) for large adenomas (size > 1cm in diameter).The inverse association of the mineral score and risk of adenomas was also more pronounced (highest mineral score tertile vs. lowest mineral score tertile OR=0.54, 95% CI: 0.29, 1.02, P_{trend}=0.06) for adenomas with moderate or severe histological dysplasia. Similar patterns of findings were observed in the comparisons with the community controls.

Discussion

The data presented suggest that a higher combined mineral intake score (higher intakes of magnesium, copper, zinc, calcium and lower intakes of iron) may be associated with lower risk of advanced incident, sporadic colorectal adenomas.

There is biologic plausibility and animal experimental evidence for protection against colorectal adenomas by magnesium, copper, zinc and calcium. The proposed mechanisms for magnesium include maintaining genome stability (65), the potential for binding bile acids, thus preventing mutations in colonic epithelial cells (66), and its effect

on attenuating oxidative stress (3). The proposed mechanisms for copper and zinc are their being essential components of the Cu, Zn-SOD (76-78), an antioxidative enzyme (79). Other proposed mechanisms for zinc include inhibiting proliferation of colorectal cancer cells through activation of extracellular signal regulated kinases (ERKs) (86) and preventing the generation of strong oxidants by inhibiting NADPH oxidases. The proposed mechanisms for calcium against colorectal adenomas include binding bile acids and fatty acids (118, 119), direct effects on cell cycle regulation, modulation of oxidative stress (107) and the APC colon carcinogenesis pathway through modulating the expression of E-cadherin and β-catenin via the calcium-sensing receptor (52).

Our findings are consistent with much of the data available from previous studies on intakes of magnesium, copper, zinc and colorectal cancer risk. Four of the five prospective studies that evaluated the magnesium intakes and colorectal cancer risk reported an inverse association (68-71, 74). Our results are also consistent with a case-control study that reported an inverse association between total intake of magnesium and colorectal adenomas (highest tertile vs. lowest tertile OR=0.54, 95% CI: 0.36, 0.82, $P_{trend} < 0.01$) (12). Although our results on magnesium were not statistically significant, a lower risk of adenoma was observed among those with higher intakes of magnesium in the comparisons involving both control groups. Associations between intakes of copper, zinc and colorectal adenomas have been rarely reported and there have been few epidemiologic studies on copper and zinc intake and colorectal cancers (82-84, 95, 98) However, consistent with our findings on copper intake, two of the three available observational studies found an inverse association of copper intakes with colorectal cancer. For example, a case-control study in a Portuguese population observed a

statistically significant 60% decrease in risk of colorectal cancer among those in the highest quartile of copper intake compared to those in the lowest quartile (83). Another case control study that investigated dietary patterns and colon cancer risk in Hong Kong found that copper may be a independent protective agent against colon cancer (82). Our results on zinc intake are also consistent with those from the Swedish Mammography Cohort, which reported no statistically significant linear association between zinc intake and colon cancer risk (95). There is substantial evidence that calcium reduces the risk of adenomas. Eleven out of 15 observational studies of calcium intakes and colorectal adenomas reported a non-significant inverse association (113, 120-130), three reported a statistically significant association (131-133), and the remaining two reported a positive association (134, 135). A meta-analysis of randomized controlled trials found that supplemental calcium was effective for the prevention of adenoma recurrence (91). We did not find a strong inverse association of calcium and adenomas, but in the comparison with community controls, a non-significant inverse association was observed.

Observational studies that investigated total intake of iron and colorectal adenomas have been inconsistent, although iron, particularly, heme iron, is hypothesized to be pro-oxidant and to damage DNA by free radicals generated through the Fenton reaction (93). We found no associations; this is consistent with some of the previous studies on iron intake and colorectal adenoma risk (97, 99, {Hoff, 1986 #2154, 135-139).

The inverse association between the combined mineral score and colorectal adenomas observed was stronger among individuals with more advanced colorectal lesions, characterized by large size, multiple adenomas, adenomas with villous histology, or moderate or severe dysplasia. This suggests that minerals may play a more pronounced

role in reducing risk for adenoma progression than their genesis. Vegetables are one of the major sources of most minerals. This finding is consistent with the previously published results from this same case-control study, which indicated a stronger association of vegetables with advanced adenomas than with early adenomas (140). This is also consistent with findings from other studies. Benito et al reported a statistically significant inverse association between vegetable intake and risk of large size (larger than 1 cm in diameter) of adenomas (136). Millen et al. found a stronger inverse association between total vegetables without potatoes and risk of advanced adenoma and multiple adenomas (141).

Animal studies suggest that the contribution of deficiency of certain antioxidants to chronic inflammation and oxidant stress can be compensated for by increased intake of other antioxidants (142, 143). It is possible that high intake of antioxidant-related minerals may emolliate the effect of low intake of other anti-oxidants on inflammation and oxidative stress. Our findings in the analysis involving the colonoscopy-negative controls did support the hypothesis that there may be a stronger inverse association among individuals with a low oxidative balance score.

Bile acids are implicated as etiologic agents in colorectal cancer. Magnesium and calcium are able to bind bile acids (a product of digesting fats) in the colonial lumen, which is considered one of the possible mechanisms for their role in colorectal carcinogenesis. Therefore, we hypothesized that there may be a more pronounced inverse association for mineral scores among individuals with high fat intakes. The data in this study did not support this hypothesis.

One of the strength of this study was that a composite mineral score was used to summarize the level of mineral exposures. Besides the difficulty of measuring the intakes of minerals by food frequency questionnaires, one possible explanation for the inconsistent results found in previous studies is that there is close interrelationships between these minerals, including antagonisms and synergisms. Antagonism often occurs on the absorption level; for example, a high intake of calcium may suppress the absorption of zinc in the GI tract, and a high zinc intake can suppress copper intake. The antagonism between zinc and copper is also seen on the metabolic level. On the other hand, synergism between the elements usually occurs on a metabolic level. Sufficient copper is needed for iron metabolism. There is also antagonism between magnesium and calcium (13). Minerals may also inhibit or enhance the effects of other minerals. As an example, animal studies found that calcium inhibited heme-induced cytotoxicity and prevented heme-induced colonic epithelial hyperproliferation (105, 144). Animal models also found that signs of magnesium deficiency can be alleviated by high intakes of other antioxidant-related micronutrients (145). The score method is a simple way of summarizing overall mineral exposure while taking the interrelations among minerals into consideration.

Another strength of this study was that there were two control groups. The colonoscopy control group underwent colonoscopy and was determined to be adenoma-free. However, these individuals may have been higher risk and thus more similar to the cases, since participants in these two groups had an indication for colonoscopy. In fact, as shown in Table 1, their lifestyle factors were similar. The community control group, on the other hand, was more representative of the general population, but some community

controls may have had undiagnosed adenomas. However, the limitations of the two control groups would tend to attenuate true associations.

The study had several limitations. One limitation was that the score method used in the analysis was based on the assumption that all the mineral exposures have effects of similar magnitude. This assumption is questionable. The method may require further refinement. Another limitation is that total iron intake was used. The effect of total iron intake remains controversial, whereas heme iron intake may be the more detrimental form of iron exposure.

In conclusion, our findings, taken together with previous literature, suggest that a higher combined mineral intake (higher intakes of magnesium, copper, zinc, calcium and lower intakes of iron) may be associated with a lower risk of advanced incident, sporadic colorectal adenomas. Further study of the potential role of mineral intakes in colorectal carcinogenesis may be needed.

CHAPTER 3. FUTURE DIRECTIONS

Conclusions and public health implications

This study was conducted to evaluation the associations of magnesium, copper, zinc, calcium, and iron intakes separately as well as a composite mineral score representing higher intakes of magnesium, copper, zinc, calcium and lower intakes of iron with risk for colorectal adenomas. Our data suggested that a higher combined mineral intake score may be associated with a lower risk of advanced of incident, sporadic colorectal adenomas.

Colorectal cancer is the second most common cause of cancer-related mortality in the U.S. Our findings indicate that a balanced diet rich in anti-oxidant-related minerals may benefit people with advanced adenomas. Given the extent of colorectal cancer, the observation may have sizable potential public health implications. It is estimated that 56 % of Americans fail to consume adequate amount of magnesium, and12% of them do not have adequate zinc intake, especially among persons aged >71 years (30% for males, 36% for females) who are also at a higher risk of colorectal cancer (60). Therefore, the public health agencies should develop strategies to increase awareness of balanced eating, and to identify and prevent mineral deficiency particularly of magnesium and zinc in the general population.

Future directions

In addition to demographic and lifestyle factors investigated in this study, genetic factors may be considered as potential effect modifiers of the association of mineral intakes with colorectal adenomas. For example, in the study by Dai et al, the researchers found that

people who carried a genetic variant of the transient receptor potential melastatin 7 (TRPM7) may have a higher risk of colorectal neoplasia since they are at a higher risk of magnesium deficiency (12). Further studies in genetic variants involved in the minerals uptakes and the oxidative stress pathways involving these minerals may be needed.

The score method may need to be refined according to their relative contribution to the process of oxidative stress, since the assumption that the effect mineral exposures are of similar magnitude may not be valid. The magnitude of the association of the individual mineral can be estimated by systematic reviews or meta-analyses of observational studies and clinical trials. The values representing the high and low exposure of the individual mineral will be determined by the summary association obtained from systematic reviews or meta-analyses.

TABLES

Table 1. Selected characteristics of colorectal adenoma cases, colonoscopy negative controls, and community controls in Minnesota Cancer Prevention Research Unit, United States, 1991-1994.

Characteristics	Adenoma cases N=566	Colonoscopy-negative Controls N=687	Community controls N=536	P* cases vs colonoscopy-negative controls	P* cases vs community controls
Age, y	58.1 (9.6)	52.8 (11.0)	57.7 (10.4)	<.0001	0.34
Men (%)	62	38	55	<.0001	0.03
White (%)	98	97	97	0.50	0.64
College graduate (%)	30	30	30	0.13	0.13
Family history of colorectal cancer[$] (%)	20	34	9	<.0001	<.0001
Total MET hours of physical activity/week	261.1 (275.6)	234.4 (217.7)	267.2 (274.1)	0.55	0.56
Take NSAID†regularly (%)	12	21	17	<.0001	0.01
Take aspirin† regularly (%)	28	31	30	0.28	0.64
If a woman(n=885), HRT use (%)	40	51	45	0.005	0.27
Current smoker (%)	21	15	15	<.0001	0.002
BMI, kg/m^2	27.4 (4.7)	26.9 (5.0)	26.8 (4.5)	0.07	0.05
Total energy intake, kcal/d	2088.7 (775.2)	2017.0 (719.4)	2052.4 (720.3)	0.14	0.61
Total retinol, IU/d	3035.5 (3006.0)	3288.2 (3720.9)	3547.3 (3736.7)	0.50	0.03
Total folate, µg/d	398.6 (236.7)	412.7 (241.0)	429.3 (250.0)	0.38	0.02
Total red meat and processed meat intake, servings/d	7.3 (6.1)	6.7 (5.3)	6.9 (5.6)	0.34	0.41
Alcohol, mg/d	10 (16.5)	6.5 (13.3)	8.1 (15.5)	<.0001	0.01

Table continues

Table 1. continued.

Intake of fruits and vegetables, serving/wk	42.3 (23.8)	43.9 (26.2)	44.5 (23.5)	0.27	0.03
Total vitamin C[‡] intake,mg/d	246.7 (295.8)	276.5 (307.4)	262.7 (295.2)	0.04	0.13
Total magnesium[‡]intake, mg/d	326.0 (123.3)	317.4 (117.1)	334.6 (126.9)	0.27	0.24
Total Zinc[‡] intake, mg/d	16.7 (14.8)	15.9 (12.1)	16.5 (12.2)	0.40	0.87
Total copper[‡] intake, mg/d	1.7 (0.8)	1.7 (0.8)	1.8 (0.9)	0.40	0.04
Total iron[‡] intake, mg/d	18.5 (14.9)	20.5 (18.8)	18.3 (11.9)	0.16	0.55
Total calcium[‡ intake], mg/d	957.7 (531.0)	984.9 (525.6)	986.8 (552.2)	0.25	0.34
Oxidant balance score (OBS) [**]	4.2 (2.2)	4.3 (2.1)	4.6 (2.1)	0.36	0.001
Mineral score[**]	2.4 (1.3)	2.5 (1.3)	2.5 (1.3)	0.33	0.40

NOTE: Data are given as means (SD) unless otherwise specified.

Abbreviation: BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug; MET, metabolic equivalent task; HRT: hormone replacement therapry.

*By Fisher's exact $\chi 2$ test for categorical variables and ANOVA for continuous variables

$ Family history of colorectal cancer in a first degree relative.

[†] At least weekly.

[‡] Diet plus supplements

[§] At least two adenomas.

** see text for full detail.

Table 2. Crude and multivariate-adjusted associations of separate and combined mineral intakes with colorectal adenoma; Minnesota Cancer Prevention Research Unit, United States, 1991-1994.

Daily mineral intake quintiles and mineral score[c]	Colonoscopy-negative control				Community control			
	Crude OR	95% CI	Multivariate adjusted OR[a]	95% CI[a]	Crude OR	95% CI	Multivariate adjusted OR[b]	95% CI[b]
Magnesium								
1	1.00		1.00		1.00		1.00	
2	0.76	(0.55,1.05)	0.74	(0.48,1.14)	0.57	(0.41,0.81)	0.59	(0.38,0.91)
3	1.13	(0.84,1.51)	0.96	(0.60,1.53)	0.93	(0.67,1.28)	0.81	(0.51,1.30)
4	0.95	(0.70,1.30)	0.86	(0.44,1.68)	0.68	(0.49,0.95)	0.61	(0.32,1.17)
P_{trend}	0.79		0.84		0.14		0.28	
Copper								
1	1.00		1.00		1.00		1.00	
2	1.31	(0.95,1.79)	1.21	(0.79,1.85)	0.85	(0.61,1.18)	0.78	(0.51,1.19)
3	1.00	(0.74,1.35)	0.96	(0.60,1.54)	0.93	(0.67,1.30)	0.85	(0.52,1.37)
4	0.90	(0.66,1.24)	0.63	(0.35,1.16)	0.71	(0.51,1.00)	0.54	(0.30,0.97)
P_{trend}	0.27		0.04		0.05		0.03	
Zinc								
1	1.00		1.00		1.00		1.00	
2	1.00	(0.74,1.37)	0.97	(0.64,1.46)	1.01	(0.73,1.41)	1.14	(0.75,1.73)
3	0.77	(0.56,1.05)	0.82	(0.51,1.32)	0.85	(0.61,1.19)	0.97	(0.61,1.57)
4	0.96	(0.70,1.32)	1.24	(0.71,2.18)	0.91	(0.65,1.27)	0.90	(0.53,1.54)
P_{trend}	0.99		0.30		0.46		0.51	

Table continue

Table 2. continued.

Iron								
1	1.00		1.00		1.00		1.00	
2	0.90	(0.65,1.24)	1.06	(0.69,1.63)	0.67	(0.48,0.95)	0.83	(0.55,1.27)
3	0.97	(0.71,1.31)	1.15	(0.72,1.82)	0.87	(0.63,1.20)	0.98	(0.62,1.56)
4	0.87	(0.64,1.18)	1.09	(0.66,1.83)	0.80	(0.58,1.12)	1.04	(0.61,1.77)
P_{trend}	0.43		0.85		0.51		0.66	
Calcium								
1	1.00		1.00		1.00		1.00	
2	0.91	(0.66,1.25)	0.78	(0.51,1.19)	0.86	(0.62,1.20)	0.73	(0.48,1.11)
3	0.74	(0.55,1.01)	0.72	(0.46,1.11)	0.88	(0.63,1.22)	0.91	(0.59,1.42)
4	0.93	(0.68,1.27)	1.14	(0.68,1.91)	0.87	(0.62,1.21)	0.95	(0.57,1.59)
P_{trend}	0.52		0.44		0.24		0.74	
Mineral score								
1	1.00		1.00		1.00		1.00	
2	0.94	(0.72,1.22)	0.83	(0.57,1.19)	0.87	(0.66,1.15)	0.84	(0.59,1.21)
3	0.79	(0.59,1.05)	0.69	(0.41,1.15)	0.79	(0.58,1.07)	0.75	(0.46,1.22)
P_{trend}	0.10		0.15		0.13		0.24	

[a] Odds ratios with 95% confidence intervals adjusted for age (continuous), sex , HRT use (only in women), regular use of NSAID or aspirin (yes or no), smoking status (current, ever, or never), family history of colorectal cancer in a first-degree relative (yes or no), total intakes of energy (continuous), alcohol (continuous), retinol (continuous), folate (continuous), red meat and processed meat (continuous), fruits and vegetables (continuous), physical activity METs(continuous).

[a] Odds ratios with 95% confidence intervals were adjusted for age (continuous), sex, HRT use (only in women), regular use of NSAID or aspirin (yes or no), smoking status (current, ever, or never),family history of colorectal cancer in a first-degree relative (yes or no), total intakes of energy (continuous), alcohol (continuous), red meat and processed meat (continuous), fruits and vegetables (continuous), vitamin C (continuous).

[c] Mineral score cut points: 1: score<2, 2: 2<=score<=3; 3, score>3; see text for full details.

Table 3. Multivariate-adjusted associations of mineral score with colorectal adenoma according to non-dietary risk factors for colorectal neoplasm; Minnesota Cancer Prevention Research Unit, United States, 1991–1994.

Adenoma and mineral score[s]	Colonoscopy-negative controls					Community controls				
	No. of Cases	No.of Controls	OR[a]	95% CI[a]	$P_{interaction}$	No. of Cases	No.of Controls	OR[b]	95% CI[b]	$P_{interaction}$
Age					0.93					0.77
Age>=Median										
1	109	73	1.00			109	87	1.00		
2	139	107	0.74	(0.44,1.23)		139	132	0.78	(0.49,1.24)	
3	90	92	0.52	(0.56,1.06)		90	99	0.71	(0.38,1.32)	
P_{trend}			0.07					0.27		
Age<Median										
1	82	138	1.00			82	73	1.00		
2	81	152	0.95	(0.57,1.56)		81	80	0.96	(0.53,1.76)	
3	65	125	0.94	(0.46,1.93)		65	65	0.68	(0.29,1.58)	
P_{trend}			0.86					0.53		
Sex					0.48					0.15
Male										
1	114	74	1.00			114	86	1.00		
2	130	102	0.66	(0.38,1.12)		130	121	0.73	(0.46,1.18)	
3	105	83	0.64	(0.30,1.36)		105	89	0.86	(0.45,1.64)	
P_{trend}			0.22					0.59		

Table continue

Table 3. continued.

Adenoma and mineral score[s]	Colonoscopy-negative controls					Community controls				
	No. of Cases	No.of Controls	OR[a]	95% CI[a]	$P_{interaction}$	No. of Cases	No.of Controls	OR[b]	95% CI[b]	$P_{interaction}$
Female										
1	77	137	1.00			77	74	1.00		
2	90	157	0.95	(0.59,1.54)		90	91	0.99	(0.56,1.76)	
3	50	134	0.69	(0.34,1.40)		50	75	0.62	(0.28,1.38)	
P_{trend}			0.36					0.21		
Obese					0.08					0.37
Yes										
1	44	52	1.00			44	23	1.00		
2	57	53	1.37	(0.66,2.85)		57	57	0.50	(0.22,1.13)	
3	42	51	0.92	(0.32,2.61)		42	37	0.55	(0.19,1.58)	
P_{trend}			0.97					0.28		
No										
1	143	152	1.00			143	136	1.00		
2	158	202	0.70	(0.45,1.05)		158	154	0.92	(0.60,1.41)	
3	112	161	0.60	(0.33,1.10)		112	125	0.75	(0.42,1.34)	
P_{trend}			0.08					0.40		

Table continues

Table 3. continued.

Adenoma and mineral score[s]	Colonoscopy-negative controls					Community controls				
	No. of Cases	No.of Controls	OR[a]	95% CI[a]	$P_{interaction}$	No. of Cases	No.of Controls	OR[b]	95% CI[b]	$P_{interaction}$
Regular use of NSAID or aspirin					0.21					0.57
Yes										
1	52	88	1.00			52	54	1.00		
2	90	117	1.17	(0.65,2.10)		90	88	0.93	(0.50,1.73)	
3	65	104	0.64	(0.29,1.43)		65	71	0.59	(0.27,1.32)	
Ptrend			0.32					0.18		
No										
1	139	123	1.00			139	106	1.00		
2	130	141	0.68	(0.42,1.10)		130	124	0.83	(0.52,1.32)	
3	90	113	0.77	(0.39,1.53)		90	92	0.95	(0.49,1.84)	
Ptrend			0.34					0.67		
Family history[d]					0.11					0.34
Yes										
1	28	47	1.00			28	9	1.00		
2	40	67	0.93	(0.42,2.05)		40	13	1.34	(0.42,4.30)	
3	24	73	0.34	(0.12,1.00)		24	15	0.77	(0.18,3.40)	
Ptrend			0.06					0.75		

Table continues

Family history[d]								
No								
1	130	118	1.00		130	109	1.00	
2	139	143	0.77	(0.51,1.17)	139	144	0.77	(0.52,1.14)
3	96	100	0.83	(0.45,1.50)	96	106	0.74	(0.43,1.26)
Ptrend			0.45				0.18	

[a] Odds ratios with 95% confidence intervals adjusted for age (continuous), sex, HRT use (only in women), regular use of NSAID or aspirin (yes or no), smoking status (current, ever, or never), family history of colorectal cancer in a first-degree relative (yes or no), total intakes of energy (continuous), alcohol (continuous), retinol (continuous), folate (continuous), red meat and processed meat (continuous), fruits and vegetables (continuous), physical activity METS (continuous).

[a] Odds ratios with 95% confidence intervals adjusted for age (continuous), sex, HRT use (only in women), regular use of NSAID or aspirin (yes or no), smoking status (current, ever, or never),family history of colorectal cancer in a first-degree relative (yes or no), total intakes of energy (continuous), alcohol (continuous), red meat and processed meat (continuous), fruits and vegetables (continuous), vitamin C (continuous).

[c] Mineral score cut points: 1:score<2, 2: 2<=score<=3; 3, score>3;

Table 4. Multivariate-adjusted associations of mineral score with colorectal adenoma by dietary factors; Minnesota Cancer Prevention Research Unit, United States, 1991–1994.

	Colonoscopy-negative controls					Community controls				
mineral score[s]	No. of Cases	No. of Controls	OR a	95% CI	$P_{interaction}$	No. of Cases	No. of Controls	OR a	95% CI	$P_{interaction}$
Total fat intake					0.35					0.09
<Median										
1	154	163	1.00			154	115	1.00		
2	110	139	0.71	(0.44,1.14)		110	111	0.69	(0.42,1.13)	
3	31	48	0.65	(0.28,1.48)		31	42	0.48	(0.21,1.13)	
P_{trend}			0.17					0.05		
>=Median										
1	37	48	1.00			37	45	1.00		
2	110	120	1.30	(0.69,2.48)		110	101	1.32	(0.70,2.49)	
3	124	169	0.91	(0.44,1.90)		124	122	1.22	(0.60,2.45)	
Ptrend			0.55					0.73		
OBS[d]					0.50					0.92
<Median										
1	148	154	1.00			148	115	1.00		
2	123	146	0.71	(0.44,1.15)		123	102	0.91	(0.56,1.50)	
3	44	69	0.46	(0.21,0.99)		44	43	0.97	(0.43,2.21)	
P_{trend}			0.04					0.70		
>=Median										
1	43	57	1.00			148	115	1.00		
2	97	113	1.17	(0.64,2.16)		123	102	0.86	(0.48,1.55)	
3	111	148	1.05	(0.50,2.21)		44	43	0.68	(0.34,1.33)	
P_{trend}			0.96					0.23		

[a] Odds ratios with 95% confidence intervals adjusted for age (continuous), sex , HRT use (only in women), regular use of NSAID or aspirin (yes or no), smoking status (current, ever, or never), family history of colorectal cancer in a first-degree relative (yes or not), total intakes of energy (continuous), alcohol (continuous), retinol (continuous), folate (continuous), red meat and processed meat (continuous), fruits and vegetables (continuous), physical activity METs (continuous).

[a] Odds ratios with 95% confidence intervals were adjusted for age (continuous), sex and HRT use (only in women), regular use of NSAID or aspirin (yes or no), smoking status (current, ever, or never), family history of colorectal cancer in a first-degree relative (yes or not), total intakes of energy (continuous), alcohol (continuous), red meat and processed meat (continuous), fruits and vegetables (continuous), vitamin C (continuous).

[c] Mineral score cut points: 1: score<2, 2: 2<=score<=3; 3, score>3;

Table 5. Multivariable-adjusted associations of mineral scores with colorectal adenomas according to adenoma characteristics; Minnesota Cancer Prevention Research Unit, United States, 1991-1994.

Adenoma characteristics and mineral scores[c]	Colonoscopy-negative controls				Community controls			
	No. of Case	No. of Controls	OR[a]	95% CI	No. of Case	No. of Controls	OR[b]	95% CI
Location								
Right colon								
1	58	211	1.00		58	160	1.00	
2	66	259	0.74	(0.42,1.30)	66	212	0.79	(0.46,1.36)
3	46	217	0.43	(0.19,0.98)	46	164	0.67	(0.32,1.38)
P trend			0.05				0.27	
Left colon								
1	158	211	1.00		158	160	1.00	
2	191	259	0.83	(0.57,1.21)	191	212	0.91	(0.63,1.32)
3	128	217	0.71	(0.41,1.20)	128	164	0.80	(0.49,1.33)
P trend			0.19				0.39	
Multiplicity								
Multiple adenomas								
1	60	211	1.00		60	160	1.00	
2	73	259	0.74	(0.44,1.25)	73	212	0.97	(0.58,1.62)
3	41	217	0.35	(0.16,0.78)	41	164	0.74	(0.36,1.49)
P trend			0.01				0.43	
single adenoma								
1	131	211	1.00		131	160	1.00	
2	147	259	0.84	(0.56,1.24)	147	212	0.78	(0.52,1.17)
3	114	217	0.86	(0.49,1.51)	114	164	0.77	(0.45,1.31)
P trend			0.55				0.31	

Table continues

Table 5 continued.

Adenoma characteristics and mineral scores[c]	Colonoscopy-negative controls				Community controls			
	No. of Case	No. of Controls	OR[a]	95% CI	No. of Case	No. of Controls	OR[b]	95% CI
Size								
Large adenoma ≥1cm								
1	53	211	1.00		53	160	1.00	
2	69	259	0.73	(0.43,1.24)	69	212	0.95	(0.56,1.61)
3	39	217	0.51	(0.23,1.11)	39	164	0.78	(0.38,1.60)
Ptrend			0.09				0.51	
Small adenoma								
1	138	211	1.00		138	160	1.00	
2	151	259	0.82	(0.55,1.22)	151	212	0.81	(0.54,1.20)
3	116	217	0.73	(0.41,1.28)	116	164	0.76	(0.45,1.29)
P trend			0.51				0.28	
Histologic type								
Villous or tubulovillous								
1	63	211	1.00		63	160	1.00	
2	79	259	0.84	(0.50,1.40)	79	212	1.00	(0.60,1.67)
3	48	217	0.60	(0.28,1.28)	48	164	0.85	(0.42,1.69)
P trend			0.20				0.66	
Tubular								
1	126	211	1.00		126	160	1.00	
2	141	259	0.80	(0.53,1.19)	141	212	0.78	(0.53,1.17)
3	107	217	0.71	(0.40,1.25)	107	164	0.74	(0.44,1.27)
P trend			0.22				0.25	

Table continues

Table 5 continued.

Adenoma characteristics and mineral scores[c]	Colonoscopy-negative controls				Community controls			
	No. of Case	No. of Controls	OR[a]	95% CI	No. of Case	No. of Controls	OR[b]	95% CI
Degree of atyia of the worst adenoma								
Moderate/severe								
1	108	211	1.00		108	160	1.00	
2	124	259	0.80	(0.52,1.23)	124	212	0.90	(0.59,1.38)
3	69	217	0.54	(0.29,1.02)	69	164	0.72	(0.40,1.29)
P trend			0.06				0.28	
Mild								
1	75	211	1.00		75	160	1.00	
2	91	259	0.82	(0.51,1.30)	91	212	0.80	(0.50,1.27)
3	81	217	0.89	(0.46,1.71)	81	164	0.86	(0.47,1.57)
Ptrend			0.66				0.60	

[a] Odds ratios with 95% confidence intervals adjusted for age (continuous), sex , HRT use (only in women), regular use of NSAID or aspirin (yes or no), smoking status (current, ever, or never),family history of colorectal cancer in a first-degree relative (yes or no), total intakes of energy(continuous), alcohol (continuous), retinol (continuous), folate (continuous), red meat and processed meat (continuous), fruits and vegetables (continuous), physical activity METs (continuous).

[a] Odds ratios with 95% confidence intervals were adjusted for age (continuous), sex, HRT use (only in women), regular use of NSAID or aspirin (yes or no), smoking status (current, ever, or never),family history of colorectal cancer in a first-degree relative (yes or no), total intakes of energy (continuous), alcohol (continuous), red meat and processed meat (continuous), fruits and vegetables (continuous), vitamin C (continuous).

[c] Mineral score cut points: 1:score<2, 2: 2<=score<=3; 3, score>3;

REFERENCES

1. Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. *CA Cancer J Clin* 2010;60(5):277-300.
2. Miller PE, Lesko SM, Muscat JE, et al. Dietary patterns and colorectal adenoma and cancer risk: a review of the epidemiological evidence. *Nutr Cancer* 2010;62(4):413-24.
3. Hans CP, Chaudhary DP, Bansal DD. Effect of magnesium supplementation on oxidative stress in alloxanic diabetic rats. *Magnes Res* 2003;16(1):13-9.
4. Dovhanj J, Kljaic K, Dodig-Curkovic K, et al. Helicobacter pylori, zinc and iron in oxidative stress-induced injury of gastric mucosa. *Mini Rev Med Chem* 2009;9(1):26-30.
5. Gaetke LM, Chow CK. Copper toxicity, oxidative stress, and antioxidant nutrients. *Toxicology* 2003;189(1-2):147-63.
6. Speich M, Pineau A, Ballereau F. Minerals, trace elements and related biological variables in athletes and during physical activity. *Clin Chim Acta* 2001;312(1-2):1-11.
7. Chua AC, Klopcic B, Lawrance IC, et al. Iron: an emerging factor in colorectal carcinogenesis. *World J Gastroenterol* 2010;16(6):663-72.
8. Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* 2006;354(7):684-96.
9. Carruthers C, Suntzeff V. Calcium, copper, and zinc in the epidermal carcinogenesis of mouse and man. *Cancer Res* 1946;6:296.

10. Giovannucci E. Calcium plus vitamin D and the risk of colorectal cancer. *N Engl J Med* 2006;354(21):2287-8; author reply -8.

11. Cho E, Smith-Warner SA, Spiegelman D, et al. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. *J Natl Cancer Inst* 2004;96(13):1015-22.

12. Dai Q, Shrubsole MJ, Ness RM, et al. The relation of magnesium and calcium intakes and a genetic polymorphism in the magnesium transporter to colorectal neoplasia risk. *Am J Clin Nutr* 2007;86(3):743-51.

13. Pusateri DJ, Roth WT, Ross JK, et al. Dietary and Hormonal Evaluation of Men at Different Risks for Prostate-Cancer - Plasma and Fecal Hormone-Nutrient Interrelationships. *American Journal of Clinical Nutrition* 1990;51(3):371-7.

14. Society AC. Cancer facts & figures 2010 [electronic article].

15. Potter JD, Slattery ML, Bostick RM, et al. Colon cancer: a review of the epidemiology. *Epidemiologic Reviews* 1993;15(2):499-545.

16. Center MM, Jemal A, Smith RA, et al. Worldwide variations in colorectal cancer. *CA Cancer J Clin* 2009;59(6):366-78.

17. Center MM, Jemal A, Ward E. International trends in colorectal cancer incidence rates. *Cancer Epidemiol Biomarkers Prev* 2009;18(6):1688-94.

18. Flood DM, Weiss NS, Cook LS, et al. Colorectal cancer incidence in Asian migrants to the United States and their descendants. *Cancer Causes Control* 2000;11(5):403-11.

19. Morson BC. Genesis of colorectal cancer. *Clin Gastroenterol* 1976;5(3):505-25.

20. Peltomaki P. Deficient DNA mismatch repair: a common etiologic factor for colon cancer. *Hum Mol Genet* 2001;10(7):735-40.

21. Moran A, Ortega P, de Juan C, et al. Differential colorectal carcinogenesis: Molecular basis and clinical relevance. *World J Gastrointest Oncol* 2010;2(3):151-8.

22. Research AIfC. Reducing your risk of colorectal cancer. Washington, (Research AIfC

23. Wolin KY, Yan Y, Colditz GA, et al. Physical activity and colon cancer prevention: a meta-analysis. *Br J Cancer* 2009;100(4):611-6.

24. Wolin KY, Lee IM, Colditz GA, et al. Leisure-time physical activity patterns and risk of colon cancer in women. *Int J Cancer* 2007;121(12):2776-81.

25. Harriss DJ, Atkinson G, Batterham A, et al. Lifestyle factors and colorectal cancer risk (2): a systematic review and meta-analysis of associations with leisure-time physical activity. *Colorectal Dis* 2009;11(7):689-701.

26. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. *Am J Clin Nutr* 2007;86(3):556-65.

27. Dai Z, Xu YC, Niu L. Obesity and colorectal cancer risk: a meta-analysis of cohort studies. *World J Gastroenterol* 2007;13(31):4199-206.

28. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;371(9612):569-78.

29. Fedirko V, Tramacere I, Bagnardi V, et al. Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. *Ann Oncol* 2011.

30. Liang PS, Chen TY, Giovannucci E. Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. *Int J Cancer* 2009;124(10):2406-15.

31. Chen K, Qiu JL, Zhang Y, et al. Meta analysis of risk factors for colorectal cancer. *World J Gastroenterol* 2003;9(7):1598-600.

32. Botteri E, Iodice S, Raimondi S, et al. Cigarette smoking and adenomatous polyps: A meta-analysis. *Gastroenterology* 2008;134(2):388-95.

33. Yamasaki E, Ames BN. Concentration of mutagens from urine by absorption with the nonpolar resin XAD-2: cigarette smokers have mutagenic urine. *Proc Natl Acad Sci U S A* 1977;74(8):3555-9.

34. Kune GA, Kune S, Vitetta L, et al. Smoking and colorectal cancer risk: data from the Melbourne Colorectal Cancer Study and brief review of literature. *Int J Cancer* 1992;50(3):369-72.

35. Rostom A, Dube C, Lewin G, et al. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. *Ann Intern Med* 2007;146(5):376-89.

36. Dube C, Rostom A, Lewin G, et al. The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. *Ann Intern Med* 2007;146(5):365-75.

37. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med* 1999;106(5):574-82.

38. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291(14):1701-12.

39. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med* 2004;350(10):991-1004.

40. Wu AH, Siegmund KD, Long TI, et al. Hormone therapy, DNA methylation and colon cancer. *Carcinogenesis* 2010;31(6):1060-7.

41. Issa JP, Ottaviano YL, Celano P, et al. Methylation of the oestrogen receptor CpG island links ageing and neoplasia in human colon. *Nat Genet* 1994;7(4):536-40.

42. Alexander DD, Miller AJ, Cushing CA, et al. Processed meat and colorectal cancer: a quantitative review of prospective epidemiologic studies. *Eur J Cancer Prev* 2010;19(5):328-41.

43. Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. *Int J Cancer* 2006;119(11):2657-64.

44. Norat T, Lukanova A, Ferrari P, et al. Meat consumption and colorectal cancer risk: dose-response meta-analysis of epidemiological studies. *Int J Cancer* 2002;98(2):241-56.

45. Stavric B. Biological significance of trace levels of mutagenic heterocyclic aromatic amines in human diet: a critical review. *Food Chem Toxicol* 1994;32(10):977-94.

46. Cross AJ, Ferrucci LM, Risch A, et al. A Large Prospective Study of Meat Consumption and Colorectal Cancer Risk: An Investigation of Potential Mechanisms Underlying this Association. *Cancer Research* 2010;70(6):2406-14.

47. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. II. Mechanisms. *Cancer Causes Control* 1991;2(6):427-42.

48. Koushik A, Hunter DJ, Spiegelman D, et al. Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies. *J Natl Cancer Inst* 2007;99(19):1471-83.

49. Lanza E, Yu B, Murphy G, et al. The polyp prevention trial continued follow-up study: no effect of a low-fat, high-fiber, high-fruit, and -vegetable diet on adenoma recurrence eight years after randomization. *Cancer Epidemiol Biomarkers Prev* 2007;16(9):1745-52.

50. Kim DH, Smith-Warner SA, Spiegelman D, et al. Pooled analyses of 13 prospective cohort studies on folate intake and colon cancer. *Cancer Causes Control* 2010;21(11):1919-30.

51. Sanjoaquin MA, Allen N, Couto E, et al. Folate intake and colorectal cancer risk: a meta-analytical approach. *Int J Cancer* 2005;113(5):825-8.

52. Lamprecht SA, Lipkin M. Chemoprevention of colon cancer by calcium, vitamin D and folate: molecular mechanisms. *Nat Rev Cancer* 2003;3(8):601-14.

53. Lamprecht SA, Lipkin M. Cellular mechanisms of calcium and vitamin D in the inhibition of colorectal carcinogenesis. *Ann N Y Acad Sci* 2001;952:73-87.

54. Bostick RM, Potter JD, McKenzie DR, et al. Reduced risk of colon cancer with high intake of vitamin E: the Iowa Women's Health Study. *Cancer Res* 1993;53(18):4230-7.

55. Welch AA, Fransen H, Jenab M, et al. Variation in intakes of calcium, phosphorus, magnesium, iron and potassium in 10 countries in the European Prospective Investigation into Cancer and Nutrition study. *Eur J Clin Nutr* 2009;63 Suppl 4:S101-21.

56. Hopkins MH, Fedirko V, Jones DP, et al. Antioxidant micronutrients and biomarkers of oxidative stress and inflammation in colorectal adenoma patients: results from a randomized, controlled clinical trial. *Cancer Epidemiol Biomarkers Prev* 2010;19(3):850-8.

57. Ames BN, Wakimoto P. Are vitamin and mineral deficiencies a major cancer risk? *Nat Rev Cancer* 2002;2(9):694-704.

58. Vormann J. Magnesium: nutrition and metabolism. *Mol Aspects Med* 2003;24(1-3):27-37.

59. Laires MJ, Monteiro CP, Bicho M. Role of cellular magnesium in health and human disease. *Frontiers in Bioscience* 2004;9:262-76.

60. Moshfegh A GJ, Ahuja J, Rodes D, LaComb R. What We Eat in America, NHANES 2005–2006: Usual Nutrient Intakes from Food and Water Compared to 1997 Dietary Reference Intakes for Vitamin D, Calcium, Phosphorus, and Magnesium. Agricultural Research Service, 2009.

61. Bo S, Durazzo M, Guidi S, et al. Dietary magnesium and fiber intakes and inflammatory and metabolic indicators in middle-aged subjects from a population-based cohort. *Am J Clin Nutr* 2006;84(5):1062-9.

62. Song Y, Li TY, van Dam RM, et al. Magnesium intake and plasma concentrations of markers of systemic inflammation and endothelial dysfunction in women. *Am J Clin Nutr* 2007;85(4):1068-74.

63. Chacko SA, Song Y, Nathan L, et al. Relations of dietary magnesium intake to biomarkers of inflammation and endothelial dysfunction in an ethnically diverse cohort of postmenopausal women. *Diabetes Care* 2010;33(2):304-10.

64. King DE, Mainous AG, 3rd, Geesey ME, et al. Dietary magnesium and C-reactive protein levels. *J Am Coll Nutr* 2005;24(3):166-71.

65. Wang A, Yoshimi N, Tanaka T, et al. Inhibitory effects of magnesium hydroxide on c-myc expression and cell proliferation induced by methylazoxymethanol acetate in rat colon. *Cancer Lett* 1993;75(2):73-8.

66. Wang A, Yoshimi N, Tanaka T, et al. The inhibitory effect of magnesium hydroxide on the bile acid-induced cell proliferation of colon epithelium in rats with comparison to the action of calcium lactate. *Carcinogenesis* 1994;15(11):2661-3.

67. Barbagallo M, Dominguez LJ, Resnick LM. Insulin-mimetic action of vanadate - Role of intracellular magnesium. *Hypertension* 2001;38(3):701-4.

68. Larsson SC, Bergkvist L, Wolk A. Magnesium intake in relation to risk of colorectal cancer in women. *Jama-Journal of the American Medical Association* 2005;293(1):86-9.

69. Ma E, Sasazuki S, Inoue M, et al. High Dietary Intake of Magnesium May Decrease Risk of Colorectal Cancer in Japanese Men. *Journal of Nutrition* 2010;140(4):779-85.

70. Folsom AR, Hong CP. Magnesium intake and reduced risk of colon cancer in a prospective study of women. *American Journal of Epidemiology* 2006;163(3):232-5.

71. van den Brandt PA, Smits KM, Goldbohm RA, et al. Magnesium intake and colorectal cancer risk in the Netherlands Cohort Study. *British Journal of Cancer* 2007;96(3):510-3.

72. Yang CY, Chiu HF. Calcium and magnesium in drinking water and risk of death from rectal cancer. *International Journal of Cancer* 1998;77(4):528-32.

73. Yang CY, Chiu HF, Chiu JF, et al. Calcium and magnesium in drinking water and risk of death from colon cancer. *Japanese Journal of Cancer Research* 1997;88(10):928-33.

74. Lin J, Cook NR, Lee IM, et al. Total magnesium intake and colorectal cancer incidence in women. *Cancer Epidemiology Biomarkers & Prevention* 2006;15(10):2006-9.

75. Linder MC, HazeghAzam M. Copper biochemistry and molecular biology. *American Journal of Clinical Nutrition* 1996;63(5):S797-S811.

76. Turnlund JR. Human whole-body copper metabolism. *Am J Clin Nutr* 1998;67(5 Suppl):960S-4S.

77. Turnlund JR, Keyes WR, Peiffer GL, et al. Copper absorption, excretion, and retention by young men consuming low dietary copper determined by using the stable isotope 65Cu. *Am J Clin Nutr* 1998;67(6):1219-25.

78. Turnlund JR, Thompson KH, Scott KC. Key features of copper versus molybdenum metabolism models in humans. *Adv Exp Med Biol* 1998;445:271-81.

79. Theophanides T, Anastassopoulou J. Copper and carcinogenesis. *Crit Rev Oncol Hematol* 2002;42(1):57-64.

80. Gokhale NH, Padhye SS, Padhye SB, et al. Copper complexes of carboxamidrazone derivatives as anticancer agents. 3. Synthesis, characterization and crystal structure of [Cu(appc)Cl-2], (appc = N-1(2-acetylpyridine)pyridine-2-carboxamidrazone). *Inorganica Chimica Acta* 2001;319(1-2):90-4.

81. Davis CD, Newman S. Inadequate dietary copper increases tumorigenesis in the Min mouse. *Cancer Lett* 2000;159(1):57-62.

82. Ho JY, ST; Lam, TH. A case-control study on environmental and familial risk factors for colorectal cancer in Hong Kong: dietary determinants of colorectal cancer risk. *Hong Kong Medical Journal* 2006;12(2):11-3.

83. Ravasco P, Monteiro-Grillo I, Marques Vidal P, et al. Nutritional risks and colorectal cancer in a Portuguese population. *Nutr Hosp* 2005;20(3):165-72.

84. Senesse P, Meance S, Cottet V, et al. High dietary iron and copper and risk of colorectal cancer: a case-control study in Burgundy, France. *Nutr Cancer* 2004;49(1):66-71.

85. Prasad AS. Zinc in human health: An update. *Journal of Trace Elements in Experimental Medicine* 1998;11(2-3):63-87.

86. Park KS, Ahn Y, Kim JA, et al. Extracellular zinc stimulates ERK-dependent activation of p21(Cip/WAF1) and inhibits proliferation of colorectal cancer cells. *Br J Pharmacol* 2002;137(5):597-607.

87. Martin Mateo MC, Martin G. Influence of metallic carcinogenesis in lung and colorectal neoplasia. Metals in neoplastic processes. *Clin Physiol Biochem* 1988;6(6):321-6.

88. Song MK, Heng MCY, Rolandelli R, et al. Possible Link between Zinc Intake and Colon Cancer. *Journal of the National Cancer Institute* 1993;85(8):667-9.

89. Varani J. Calcium, calcium-sensing receptor and growth control in the colonic mucosa. *Histol Histopathol* 2011;26(6):769-79.

90. Vinas-Salas J, Biendicho-Palau P, Pinol-Felis C, et al. Calcium inhibits colon carcinogenesis in an experimental model in the rat. *Eur J Cancer* 1998;34(12):1941-5.

91. Huncharek M, Muscat J, Kupelnick B. Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: a meta-analysis of 26,335 cases from 60 observational studies. *Nutr Cancer* 2009;61(1):47-69.

92. Carroll C, Cooper K, Papaioannou D, et al. Supplemental calcium in the chemoprevention of colorectal cancer: a systematic review and meta-analysis. *Clin Ther* 2010;32(5):789-803.

93. Sesink AL, Termont DS, Kleibeuker JH, et al. Red meat and colon cancer: Dietary heme, but not fat, has cytotoxic and hyperproliferative effects on the colonic epithelium. *Gastroenterology* 2000;118(4):A283-A.

94. Balder HF, Vogel J, Jansen MC, et al. Heme and chlorophyll intake and risk of colorectal cancer in the Netherlands cohort study. *Cancer Epidemiol Biomarkers Prev* 2006;15(4):717-25.

95. Larsson SC, Adami HO, Giovannucci E, et al. Re: Heme iron, zinc, alcohol consumption, and risk of colon cancer. *Journal of the National Cancer Institute* 2005;97(3):232-3.

96. Lee DH, Jacobs DR, Anderson KE. Re: Heme iron, zinc, alcohol consumption, and risk of colon cancer - Response. *Journal of the National Cancer Institute* 2005;97(3):233-4.

97. Tseng M, Sandler RS, Greenberg ER, et al. Dietary iron and recurrence of colorectal adenomas. *Cancer Epidemiol Biomarkers Prev* 1997;6(12):1029-32.

98. Lee DH, Anderson KE, Harnack LJ, et al. Heme iron, zinc, alcohol consumption, and colon cancer: Iowa Women's Health Study. *Journal of the National Cancer Institute* 2004;96(5):403-7.

99. Chan AT, Ma J, Tranah GJ, et al. Hemochromatosis gene mutations, body iron stores, dietary iron, and risk of colorectal adenoma in women. *J Natl Cancer Inst* 2005;97(12):917-26.

100. Levi F, Pasche C, Lucchini F, et al. Selected micronutrients and colorectal cancer. a case-control study from the canton of Vaud, Switzerland. *Eur J Cancer* 2000;36(16):2115-9.

101. Kato I, Dnistrian AM, Schwartz M, et al. Iron intake, body iron stores and colorectal cancer risk in women: a nested case-control study. *Int J Cancer* 1999;80(5):693-8.

102. Grant WB. An ecological study of cancer mortality rates including indices for dietary iron and zinc. *Anticancer Research* 2008;28(3B):1955-63.

103. Kabat GC, Miller AB, Jain M, et al. A cohort study of dietary iron and heme iron intake and risk of colorectal cancer in women. *Br J Cancer* 2007;97(1):118-22.

104. Bastide NM, Pierre FHF, Corpet DE. Heme Iron from Meat and Risk of Colorectal Cancer: A Meta-analysis and a Review of the Mechanisms Involved. *Cancer Prevention Research* 2011;4(2):177-84.

105. Sesink ALA, Termont DSML, Kleibeuker JH, et al. Red meat and colon cancer: dietary haem-induced colonic cytotoxicity and epithelial hyperproliferation are inhibited by calcium. *Carcinogenesis* 2001;22(10):1653-9.

106. Hartwig A. Role of magnesium in genomic stability. *Mutat Res* 2001;475(1-2):113-21.

107. Ermak G, Davies KJ. Calcium and oxidative stress: from cell signaling to cell death. *Mol Immunol* 2002;38(10):713-21.

108. Minotti G, Aust SD. The role of iron in oxygen radical mediated lipid peroxidation. *Chem Biol Interact* 1989;71(1):1-19.

109. Whitaker D, Shilkin KB, Walters MN. Cytologic and tissue culture characteristics of asbestos-induced mesothelioma in rats. *Acta Cytol* 1984;28(2):185-9.

110. Nelson RL. Iron and colorectal cancer risk: human studies. *Nutr Rev* 2001;59(5):140-8.

111. Freudenheim JL, Graham S, Marshall JR, et al. A case-control study of diet and rectal cancer in western New York. *Am J Epidemiol* 1990;131(4):612-24.

112. Benito E, Stiggelbout A, Bosch FX, et al. Nutritional factors in colorectal cancer risk: a case-control study in Majorca. *Int J Cancer* 1991;49(2):161-7.

113. Boyapati SM, Bostick RM, McGlynn KA, et al. Calcium, vitamin D, and risk for colorectal adenoma: dependency on vitamin D receptor BsmI polymorphism and nonsteroidal anti-inflammatory drug use? *Cancer Epidemiol Biomarkers Prev* 2003;12(7):631-7.

114. Gong YL, Xie DW, Deng ZL, et al. Vitamin D receptor gene Tru9I polymorphism and risk for incidental sporadic colorectal adenomas. *World J Gastroenterol* 2005;11(31):4794-9.

115. Goodman M, Bostick RM, Dash C, et al. Hypothesis: oxidative stress score as a combined measure of pro-oxidant and antioxidant exposures. *Ann Epidemiol* 2007;17(5):394-9.

116. Fedirko V, Bostick RM, Long Q, et al. Effects of supplemental vitamin D and calcium on oxidative DNA damage marker in normal colorectal mucosa: a randomized clinical trial. *Cancer Epidemiol Biomarkers Prev* 2010;19(1):280-91.

117. Goodman M, Bostick RM, Dash C, et al. A summary measure of pro- and anti-oxidant exposures and risk of incident, sporadic, colorectal adenomas. *Cancer Causes Control* 2008;19(10):1051-64.

118. Cross HS, Pavelka M, Slavik J, et al. Growth control of human colon cancer cells by vitamin D and calcium in vitro. *J Natl Cancer Inst* 1992;84(17):1355-7.

119. Newmark HL, Lipkin M. Calcium, vitamin D, and colon cancer. *Cancer Res* 1992;52(7 Suppl):2067s-70s.

120. Bonithon-Kopp C, Kronborg O, Giacosa A, et al. Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. *Lancet* 2000;356(9238):1300-6.

121. Oh K, Willett WC, Wu K, et al. Calcium and vitamin D intakes in relation to risk of distal colorectal adenoma in women. *Am J Epidemiol* 2007;165(10):1178-86.

122. Hartman TJ, Albert PS, Snyder K, et al. The association of calcium and vitamin D with risk of colorectal adenomas. *J Nutr* 2005;135(2):252-9.

123. Kesse E, Boutron-Ruault MC, Norat T, et al. Dietary calcium, phosphorus, vitamin D, dairy products and the risk of colorectal adenoma and cancer among French women of the E3N-EPIC prospective study. *International Journal of Cancer* 2005;117(1):137-44.

124. Hyman J, Baron JA, Dain BJ, et al. Dietary and supplemental calcium and the recurrence of colorectal adenomas. *Cancer Epidemiol Biomarkers Prev* 1998;7(4):291-5.

125. Peters U, Chatterjee N, McGlynn KA, et al. Calcium intake and colorectal adenoma in a US colorectal cancer early detection program(1-3). *American Journal of Clinical Nutrition* 2004;80(5):1358-65.

126. Peters U, McGlynn KA, Chatterjee N, et al. Vitamin D, calcium, and vitamin D receptor polymorphism in colorectal adenomas. *Cancer Epidemiol Biomarkers Prev* 2001;10(12):1267-74.

127. Breuer-Katschinski B, Nemes K, Marr A, et al. Colorectal adenomas and diet - A case-control study. *Digestive Diseases and Sciences* 2001;46(1):86-95.

128. Levine AJ, Harper JM, Ervin CM, et al. Serum 25-hydroxyvitamin D, dietary calcium intake, and distal colorectal adenoma risk. *Nutrition and Cancer-an International Journal* 2001;39(1):35-41.

129. Boutron MC, Faivre J, Marteau P, et al. Calcium, phosphorus, vitamin D, dairy products and colorectal carcinogenesis: A French case control study. *British Journal of Cancer* 1996;74(1):145-51.

130. Martinez ME, Giovannucci EL, Colditz GA, et al. Calcium, vitamin D, and the occurrence of colorectal cancer among women. *Journal of the National Cancer Institute* 1996;88(19):1375-82.

131. Martinez ME, Marshall JR, Sampliner R, et al. Calcium, vitamin D, and risk of adenoma recurrence (United States). *Cancer Causes Control* 2002;13(3):213-20.

132. Whelan RL, Horvath KD, Gleason NR, et al. Vitamin and calcium supplement use is associated with decreased adenoma recurrence in patients with a previous history of neoplasia. *Diseases of the Colon & Rectum* 1999;42(2):212-7.

133. Lieberman DA, Prindiville S, Weiss DG, et al. Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. *JAMA* 2003;290(22):2959-67.

134. Morimoto LM, Newcomb PA, Ulrich CM, et al. Risk factors for hyperplastic and adenomatous polyps: evidence for malignant potential? *Cancer Epidemiol Biomarkers Prev* 2002;11(10 Pt 1):1012-8.

135. Macquart-Moulin G, Riboli E, Cornee J, et al. Colorectal polyps and diet: a case-control study in Marseilles. *Int J Cancer* 1987;40(2):179-88.

136. Benito E, Cabeza E, Moreno V, et al. Diet and colorectal adenomas: a case-control study in Majorca. *Int J Cancer* 1993;55(2):213-9.

137. Little J, Logan RFA, Hawtin PG, et al. Colorectal Adenomas and Diet - a Case-Control Study of Subjects Participating in the Nottingham Fecal Occult Blood Screening-Program. *British Journal of Cancer* 1993;67(1):177-84.

138. Tseng M, Murray SC, Kupper LL. Micronutrients and the risk of colorectal adenomas (vol 144, pg 1005, 1996). *American Journal of Epidemiology* 1997;146(9):788-.

139. Hoff G, Moen IE, Trygg K, et al. Epidemiology of polyps in the rectum and sigmoid colon. Evaluation of nutritional factors. *Scand J Gastroenterol* 1986;21(2):199-204.

140. Smith-Warner SA, Elmer PJ, Fosdick L, et al. Fruits, vegetables, and adenomatous polyps: the Minnesota Cancer Prevention Research Unit case-control study. *Am J Epidemiol* 2002;155(12):1104-13.

141. Millen AE, Subar AF, Graubard BI, et al. Fruit and vegetable intake and prevalence of colorectal adenoma in a cancer screening trial. *Am J Clin Nutr* 2007;86(6):1754-64.

142. Sohet FM, Neyrinck AM, Pachikian BD, et al. Coenzyme Q10 supplementation lowers hepatic oxidative stress and inflammation associated with diet-induced obesity in mice. *Biochem Pharmacol* 2009;78(11):1391-400.

143. DeFuria J, Bennett G, Strissel KJ, et al. Dietary blueberry attenuates whole-body insulin resistance in high fat-fed mice by reducing adipocyte death and its inflammatory sequelae. *J Nutr* 2009;139(8):1510-6.

144. Pierre F, Tache S, Petit CR, et al. Meat and cancer: haemoglobin and haemin in a low-calcium diet promote colorectal carcinogenesis at the aberrant crypt stage in rats. *Carcinogenesis* 2003;24(10):1683-90.

145. Seymour EM, Lewis SK, Urcuyo-Llanes DE, et al. Regular Tart Cherry Intake Alters Abdominal Adiposity, Adipose Gene Transcription, and Inflammation in Obesity-Prone Rats Fed a High Fat Diet. *Journal of Medicinal Food* 2009;12(5):935-42.