Published in final edited form as:
Am J Clin Nutr. 2007 September ; 86(3): 743–751.

The relation of magnesium and calcium intakes and a genetic polymorphism in the magnesium transporter to colorectal neoplasia risk[1,2,3]

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Abstract

Background—Mean magnesium intake in the US population does not differ from that in East Asian populations with traditionally low risks of colorectal cancer and other chronic diseases, but the ratio of calcium to magnesium (Ca:Mg) intake is much higher in the US population. Transient receptor potential melastatin 7 (*TRPM7*) is a newly found gene essential to magnesium absorption and homeostasis.

Objective—We aimed to test whether the association of colorectal polyps with intake of calcium, magnesium, or both and Thr1482Ile polymorphism in the *TRPM7* gene is modified by the Ca:Mg intake.

Design—Included in the study were a total of 688 adenoma cases, 210 hyperplastic polyp cases, and 1306 polyp-free controls from the Tennessee Colorectal Polyp Study.

Results—We found that total magnesium consumption was linked to a significantly lower risk of colorectal adenoma, particularly in those subjects with a low Ca:Mg intake. An inverse association trend was found for hyperplastic polyps. We also found that the common *Thr1482Ile* polymorphism was associated with an elevated risk of both adenomatous and hyperplastic polyps. Moreover, this polymorphism significantly interacted with the Ca:Mg intake in relation to both adenomatous and hyperplastic polyps. The subjects who carried ≥1 *1482Ile* allele and who consumed diets with a high Ca:Mg intake were at a higher risk of adenoma (odds ratio: 1.60; 95% CI: 1.12, 2.29) and hyperplastic polyps (odds ratio: 1.85; 95% CI: 1.09, 3.14) than were the subjects who did not carry the polymorphism.

Conclusion—These findings, if confirmed, may provide a new avenue for the personalized prevention of magnesium deficiency and, thus, colorectal cancer.

Keywords

Magnesium; calcium; ratio of magnesium to calcium intake; vitamin D; colorectal adenoma

[2]Supported by grants no. P50 CA 95103 and RO1 CA97386 from the National Cancer Institute.

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INTRODUCTION

Magnesium, the second most abundant intracellular cation in the body, plays an essential role in >300 biological activities (1). Growing evidence from studies conducted in Western societies has linked a low intake of magnesium to insulin resistance (2) and systemic inflammation (3) and, thus, to the risk of diseases common in Western countries, such as colorectal cancer (4–6), type 2 diabetes (7,8), and coronary heart disease (9,10). According to data from the National Health and Nutrition Examination Survey (NHANES), 1999–2000, 79% of US adults do not meet the Recommended Dietary Allowance of magnesium (11).

Migration studies found that the incidence of the abovementioned diseases in East Asians, a group that traditionally has low risks for those diseases (12), rose after their immigration to Western societies to approach the incidence in whites (13). This finding implicates a critical role of environmental factors, particularly dietary factors. We found, however, that the mean intake of magnesium in the US population (11) does not differ significantly from and is not even slightly higher than that in the East Asian population (14,15). This suggests that low intake of magnesium per se may not be the major reason for the incidence difference. Instead, the ratio of calcium to magnesium (Ca:Mg) intake is much higher in the US population (2.8) than in the East Asian population (1.6) (14,16). Ionized magnesium (Mg^{2+}) counters the action of ionized calcium (Ca^{2+}) in many physiologic activities (17). Studies found that Mg^{2+}, the physiologic antagonist of Ca^{2+}, has the same negative feedback system—including vitamin D—as does Ca^{2+} (18,19). Studies also found that calcium directly or indirectly competes with magnesium for intestinal absorption and transport (20). A low concentration of calcium and a high concentration of magnesium (thus, a low Ca:Mg) in the lumen activates the transport of magnesium (20). In a study using the multitracer stable-isotope technique, children who consumed even the Recommended Dietary Allowance of magnesium were in negative magnesium balance if their calcium intake was high (21). An animal study found that calcium deficiency significantly reduced the elevated inflammatory responses caused by magnesium deficiency (22), which suggests the importance of the calcium-magnesium balance. Therefore, we hypothesized that a high Ca:Mg intake may exaggerate magnesium deficiency and, in turn, lead to risk of colorectal cancer.

It was not until recently that Mg^{2+} was thought to share ion channels with Ca^{2+} (18). Genetic studies found that the transient receptor potential melastatin 7 (TRPM7), a ubiquitously expressed constitutive ion channel with a higher affinity for Mg^{2+} than for Ca^{2+} (18), plays a central role in Mg^{2+} homeostasis as an Mg^{2+} uptake pathway (23). In a recent study, a missense variant [Thr-1482 to isoleucine (Ile)] in the *TRPM7* gene was not identified in controls, but was identified only in cases of Guamanian amyotrophic lateral sclerosis and parkinsonism dementia, both of which conditions have been linked to severe environmental deficiency of calcium and magnesium (24). Therefore, we postulated that people who carry the variant *Ile* allele may be at a high risk of magnesium deficiency and, in turn, of colorectal neoplasia and other chronic diseases common in the Western populations, particularly if the Ca:Mg intake is high.

To test these hypotheses, we used data from the Tennessee Colorectal Polyp Study to investigate whether the association of colorectal adenomatous and hyperplastic polyps with the intakes of calcium and magnesium or with the Thr1482Ile polymorphism in the *TRPM7* gene may be modified by the Ca:Mg intake.

SUBJECTS AND METHODS

The Tennessee Colorectal Polyp Study

Data for the current analysis were derived from the Tennessee Colorectal Polyp Study, an ongoing colonoscopy-based case-control study being conducted in Nashville, TN. Colorectal adenoma cases and polyp-free controls were recruited between February 1, 2003, and December 31, 2005. We identified 4623 eligible participants between the ages of 40 and 75 y from among persons scheduled for colonoscopy at the Vanderbilt University Gastroenterology Clinic and the Tennessee Valley Veterans Affairs Health System campus (both located in Nashville, TN); of these 4623 persons, 3094 (67%) consented to participate in the study. Excluded from our study were patients who had genetic colorectal cancer syndromes (eg, hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis), inflammatory bowel disease, or a history of adenomatous polyps or any cancer other than nonmelanoma skin cancers.

Written informed consent was obtained from all subjects. The study was approved by the institutional review boards of Vanderbilt University and the Tennessee Valley Veterans Affairs Medical Center and by the Research and Development Committee of the Department of Veterans Affairs.

A telephone interview was conducted to obtain information on lifestyle, medication use, demographics, and medical history; 87% of participants completed the telephone interview. Participants were also asked to complete a self-administered food frequency questionnaire (FFQ); 76% of participants did so. On the basis of the colonoscopy and pathology findings, participants were assigned as an adenoma case or polyp-free control. To be diagnosed as a control, the participant must have had a complete colonoscopy reaching the cecum and must have been polyp free at colonoscopy. Adenoma cases had ≥1 adenomatous polyp at colonoscopy, and hyperplastic cases had ≥1 hyperplastic polyp and no adenomas at colonoscopy. Of those who completed the telephone interviews, 98% of cases and 98% of controls donated a blood or a buccal cell sample. These samples were processed on the same day, typically within 2 h of sample collection, and were stored at −80 °C until relevant bioassays were conducted.

Dietary assessment

Participants completed a validated semi-quantitative 108-item FFQ, which was developed by using the NHANES III database at Vanderbilt University specifically to capture diet in the southern United States (25). A similar version of the FFQ is being used in the Southern Community Cohort Study with a recruitment of ≈90 000 adults for a long-term prospective cohort study of cancer and other chronic diseases. We have compared selected nutrient estimates found in the current study by using the FFQ with those found in NHANES III for Southerners aged ≥45 y by using 24-h dietary recall. We found that the intakes of energy and major nutrients did not differ significantly. For example, in NHANES III, the average daily intake (from diet only) is 1753 kcal for total energy, 671 mg for calcium, and 256 mg for magnesium, whereas, in the current study, the intakes of energy, calcium, and magnesium by controls (from diet only) are 1634 kcal, 670 mg and 256 mg, respectively. The FFQ also contains 5 items that survey eating habits and 13 items for capturing vitamin and supplement use including B vitamins, calcium, and multivitamins. The usual dietary intakes of nutrients, including those of total energy, calcium, magnesium, and vitamin D, are calculated by using data from NHANES III and US Department of Agriculture food composition tables. Calcium and magnesium intakes from calcium and multivitamin supplements were also taken into account by estimating intake on the basis of the most common ingredients in calcium and multivitamin supplements (500 mg Ca per calcium supplement pill and 162 mg Ca and 100

mg Mg per multivitamin pill). Excluded from the analyses were 19 adenoma cases, 4 hyperplastic polyp cases, and 33 controls with unreasonably high or low energy intake. As a result, a total of 688 adenoma cases, 210 hyperplastic polyp cases, and 1306 adenoma-free controls were included in the final analyses.

Genotyping assay

Genomic DNA was extracted from buffy coat fractions or cheek cells by using a QIAamp DNA mini-kit (Qiagen Inc, Valencia CA) according to the manufacturer's protocol. The allelic discrimination of the rs8042919 polymorphism in the *TRPM7* gene was assessed by using the TaqMan genotyping assay (Assay ID: C_25756319_10; Applied Biosystems, Foster City, CA). The final volume for each reaction was 5 μL, consisting of 2.5 μL TaqMan Universal PCR Master Mix (Applied Biosystems), 0.25 μL primers/TaqMan probes, and 5.0 ng genomic DNA. The polymerase chain reaction profile consisted of an initial denaturation step at 95 °C for 10 min and 40 cycles at 95 °C for 15 s and at 60 °C for 1min. Fluorescence was measured with the ABI PRISM 7900HT sequence detector (Applied Biosystems). Genotypes were determined by using ABI SDS software (version 2.1; Applied Biosystems).

The laboratory staff was blind to the identity of the subjects. Quality-control (QC) samples were included in the genotyping assays. Each 384-well plate contained 4 water blanks, 8 CEPH 1347–02 DNA, and 16 blinded QC samples. The blinded QC samples were taken from the second tube of study samples included in the study. QC samples were distributed across separate 384-well plates. The agreement rate for the genotypes of rs8042919 polymorphism with the duplicated QC samples was 99.3%. African American subjects (≈10% of total subjects) were not included in the analyses using genotyping data because these subjects were not polymorphic at rs8042919 (24). Among 603 adenoma cases, 198 hyperplastic polyp-only cases, and 1189 controls, genotyping data were obtained from 581 (96.3%), 192 (97.0%), and 1135 (95.4%), respectively. The few subjects with incomplete genotyping had insufficient DNA for the assay or unsuccessful polymerase chain reaction amplification.

Statistical analysis

Chi-square tests and *t* tests were used to evaluate case-control differences in the distribution of potential confounding factors. Unconditional logistic regression models were used to estimate odds ratios (ORs) and their 95% CIs as a measure of the strength of the association. To have a large enough sample size in subsequent stratified analyses, intakes of calcium and magnesium were categorized into tertiles on the basis of the distribution of the controls in all analyses. The first model was adjusted only for age. The second model was additionally adjusted for other confounding factors except calcium or magnesium when magnesium or calcium, respectively, was evaluated as the main association. For consistency with previous cohort studies that evaluated the association of magnesium with colon cancer (4,5), we adjusted for potential confounding factors, including dietary intake of vitamin B-6, retinol equivalents, and zinc, as well as for those factors those in Table 1, although cases and controls did not differ significantly with respect to dietary intakes of vitamin E and vitamin B-6, retinol equivalents, or zinc (data not shown). In addition, other potential confounding factors, such as the use of aspirin or of nonsteroidal antiinflammatory drugs, did not materially alter the risk estimates and thus were not adjusted for in the final model. In the third model, calcium and magnesium were further adjusted for to allow assessment of whether the association of magnesium or calcium was independent of calcium or magnesium, respectively. Stratified analyses by the Ca:Mg intake (by median), dietary intake of vitamin D (by median), and the rs8042919 genotype were conducted. Formal multiplicative interactions were also evaluated in logistic regression models by likelihood ratio tests. Although tests for interactions were of borderline significance or not statistically significant, some stratified analyses were conducted and presented on the basis of strong biological plausibility. Tests for trend across tertiles were

performed in logistic regression models by assigning the score *j* to the jth level of the variable selected. *P* values of < 0.05 (2-sided probability) were interpreted as being statistically significant. Statistical analyses were conducted by using SAS statistical software (version 9.1; SAS Institute, Cary, NC).

RESULTS

Selected demographic characteristics and potentially confounding factors were compared between cases and controls, as shown in Table 1. Compared with controls, adenomatous and hyperplastic polyp cases were more likely to be male, smokers, and alcohol drinkers and to have lower educational attainment, a higher daily dietary intakes of total energy and saturated fat, and a lower intake of total calcium. Adenomatous cases were older and more likely to have lower intakes of total magnesium, dietary vitamin D, folate, and fiber; to be physically inactive; and to have a higher BMI. In addition, hyperplastic polyp cases were significantly more likely to smoke than were adenoma cases.

The largest single contributor to magnesium intake is supplemental magnesium (51.1 mg/d, which accounts for 16.3% of total average intake). The rest of the 10 main contributors were bran or high-fiber cereals (20.6 mg); peanuts and other nuts (16.3 mg); caffeinated coffee (16.2 mg); dark or whole-grain breads (15.5 mg); low-fat milk (10.0 mg); oatmeal, cream of wheat, and other hot cereals (8.4 mg); 100% orange juice or grapefruit juice (8.3 mg); and skim milk and buttermilk (8.1 mg). The top 20 contributors to magnesium intake, including supplementation, account for 69.3% of average magnesium intake.

The overall associations, as well as the stratified associations by the median of the Ca:Mg intake, between intakes of total magnesium and calcium and the risk of colorectal adenoma are shown in Table 2. The risk of colorectal adenoma decreased with an increasing total intake of magnesium in all 3 models. Compared with the age-adjusted model, the risk was lower after adjustment for other potential confounding factors and total intake of calcium, with an OR of 0.54 (95% CI: 0.36, 0.82) in subjects who consumed total magnesium at the highest tertile versus those with the lowest intake (*P* for trend < 0.01). The association with the dietary intake of magnesium was weaker. Total intake of calcium was strongly associated with a lower risk in the age-adjusted model. After adjustments for other confounding factors, the inverse association was still of borderline significance (*P* for trend = 0.06) with an OR of 0.75 (95% CI: 0.55, 1.02). This inverse association completely disappeared, however, after additional adjustment for total magnesium intake. Dietary calcium intake was not significantly associated with colorectal adenoma risk in any model.

We conducted stratified analyses of total magnesium and calcium by the median Ca:Mg intake. We found that the inverse association of magnesium and calcium primarily appeared among those with a low Ca:Mg intake. Among those with a high Ca:Mg intake, total intake of magnesium was not related to risk, whereas total intake of calcium showed a trend toward association with a greater risk. The inverse association of magnesium with adenoma risk did not differ significantly between men and women or between proximal and distal colorectal adenoma (data not shown). We have also conducted analyses stratified by dietary intake of vitamin D (data not shown). Total magnesium intake was linked to a substantially lower adenoma risk in subjects who consumed high amounts of vitamin D and have a low Ca:Mg intake, with an OR of 0.32 (95% CI: 0.13, 0.80) comparing the highest tertile of magnesium intake with the lowest (*P* for trend < 0.01). Total calcium intake, however, may be associated with a lower risk of adenoma only when the Ca:Mg intake is low and dietary vitamin D intake is high.

The results for the association between the Thr1482Ile polymorphism in the *TRPM7* gene and colorectal adenoma (Table 3) were obtained only from non-African American subjects because African Americans were not polymorphic at this loci. The distribution of genotypes for the polymorphisms is consistent with Hardy-Weinberg equilibrium for either cases or controls. We found that the *1482Ile* allele is associated with a 20% increased risk of adenoma, although the result was of borderline significance (Table 3). Compared with those who were homozygous for 1482Thr, persons who carry ≥1 *1482Ile* allele were found to have a significantly (60%) greater risk of colorectal adenoma (OR: 1.60; 95% CI: 1.12, 2.29) if they also consumed diets with a high Ca:Mg intake. The interaction between the Thr1482Ile polymorphism and the Ca:Mg intake was statistically significant (*P* for interaction = 0.03). The overall association between intake of magnesium or calcium and the risk of adenoma in non-African American subjects (Table 4) was consistent with that in all subjects (Table 2). In subjects with ≥1 *1482Ile* allele, the inverse association with magnesium intake was further reduced, whereas high calcium intake tended to be related to an increased risk of adenoma, although the tests for interactions were not significant.

We found that the total magnesium intake may be related to a lower risk of hyperplastic polyps, as shown in Table 5, which does not differ from the findings for adenoma. The inverse association trend still existed after adjustment for total calcium intake, although the association was not significant. Again, calcium intake was significantly associated with the risk. However, there was no association in the fully adjusted model. In stratified analysis, we found that total calcium intake tended to be associated with a greater risk if the Ca:Mg intake was high (data not shown). Likewise, we found, as shown in Table 6, that, compared with those who were homozygous for 1482Thr, subjects with ≥1 *1482Ile* allele tended to be at a greater risk (OR: 1.41; 95% CI: 0.99, 2.01) of hyperplastic polyps, and the difference in risk was even greater for those subjects who consumed diets with high Ca:Mg intake (OR: 1.85; 95% CI: 1.09, 3.14).

DISCUSSION

We found in this large colonoscopy-based case-control study that, consistent with our hypotheses, the total magnesium intake is linked to a significantly lower risk of colorectal adenoma in both men and women and particularly in those with a low Ca:Mg intake and a high vitamin D intake. Likewise, total calcium intake may be associated with a lower risk of adenoma only when vitamin D intake is high and the Ca:Mg intake is low. Furthermore, an inverse association trend, although nonsignificant, was also found for hyperplastic polyps. We found that Thr1482Ile polymorphism significantly interacted with the Ca:Mg intake in relation to the risk of either adenomatous or hyperplastic polyps. Persons who carried ≥1 *1482Ile* allele were at greater risk of adenoma or hyperplastic polyps, particularly if they consumed diets with a high Ca:Mg intake. Among persons who carried ≥1 *1482Ile* allele, the inverse association with magnesium intake was further reduced, whereas high calcium intake tended to be related to a greater risk of adenoma.

Growing evidence has highlighted a potentially important role in colorectal carcinogenesis of the serrated pathway comprising hyperplastic polyps and serrated adenomas (26,27). Until recently, these polyps were mostly assumed to have no malignant potential, and, thus, few studies have evaluated risk factors for these polyps (28). Our finding of an inverse association of magnesium with colorectal adenomas or hyperplastic polyps is consistent with 2 recent cohort studies, also conducted in Western societies, in which the intake of magnesium was associated with a lower risk of colorectal cancer (4,5). The degree of reduction in the risk of adenoma or hyperplastic polyps associated with magnesium in the current study is similar to that found for colorectal cancer in 2 previous studies (12,13), which indicates that magnesium may protect against colorectal carcinogenesis at an early stage. Very recently, findings from the Netherlands Cohort Study suggest that the intake of magnesium may be associated with a

lower risk of colon cancer only in overweight subjects (6), whereas another follow-up study of participants involved in an interventional trial of aspirin and vitamin E found a null association (29). One possible explanation for the inconsistency in these previous studies is that the Ca:Mg intake is not considered.

We found that, as was consistent with our hypothesis, the intake of magnesium or calcium may be associated with a lower risk of adenoma only when the Ca:Mg intake is low and dietary vitamin D is high. Intakes of calcium and vitamin D have been inconsistently associated with the risk of colorectal cancer and adenoma in observation studies. One pooled analysis of 10 cohort studies (30) and intervention trials (31–34) suggested that high consumption of total calcium may be associated with a lower risk of adenoma and colorectal cancer, primarily in persons with a high intake of vitamin D. It is disappointing that a recent, large-scale, randomized clinical trial found that calcium plus vitamin D supplementation for 7 y had no effect on the incidence of colorectal cancer (31). One possible explanation for that negative finding is that calcium may prevent colorectal cancer development only at its earliest stage. For example, very recently, Baron et al (35) found in the observational phase of a clinical trial that the protective effect of calcium supplementation on colorectal adenoma recurrence rate extends up to 5 y after cessation of active treatment. Furthermore, in these previous studies, the potential effect modification of Ca:Mg intake was not evaluated, and that may be another possible explanation for the inconsistency of the association between calcium and colorectal cancer or adenoma (29–34,36–41). Our finding is also supported by the results from analyses using data from both the Nurses' Health Study and the Health Professionals Follow-up Study. In these 2 studies, the greatest reduction in the risks associated with calcium intake was achieved by intakes of 700–800 mg/d, but no additional reduction in risk was observed at higher calcium intakes (42). A calcium intake of >700–800 mg/d, which would probably be due to the ingestion of calcium supplements, could be linked to a higher Ca:Mg intake, which could lead to or enhance magnesium deficiency if the intake of magnesium and the bioavailability of vitamin D also are low.

Although no study has investigated the potential interaction of magnesium with calcium or vitamin D in relation to colorectal cancer or adenoma, in vitro, in vivo, and human studies indicate that calcium may directly or indirectly affect the absorption of magnesium (20,21). Furthermore, unlike calcium absorption, magnesium absorption is not entirely vitamin D dependent, although a high vitamin D concentration does aid magnesium absorption (20). Therefore, absorption of magnesium may be significantly elevated when the vitamin D intake is high and the Ca:Mg intake is low. Because calcium is more sensitive to vitamin D than is magnesium, when both Ca:Mg intake and vitamin D intake are high, the absorption of magnesium is suppressed, but calcium absorption is substantially increased. Moreover, although the changes in blood or colon lumen concentrations of ionized calcium and magnesium are monitored by the same mechanism—the calcium-sensing receptor—the potency of ionized magnesium in binding to the receptor is only one-half to one-third that of calcium (43). Therefore, once the calcium concentration is high, magnesium absorption could be significantly depressed. Moreover, it is a well-known paradoxical phenomenon that a very low or a very high concentration of ionized magnesium may inhibit parathyroid hormone secretion and, in turn, reduce the concentration of the bioactive metabolite of vitamin D (43, 44), which suggests that magnesium deficiency may subsequently cause calcium deficiency. Accordingly, when the Ca:Mg intake is high and the vitamin D intake is low, absorption of both calcium and magnesium could be suppressed simultaneously.

Many in vitro and in vivo studies found that, in addition to magnesium's potential interaction with calcium in the absorption and concentration censoring system, a high concentration of magnesium will inhibit and a deficiency of magnesium will potentiate the action of calcium in many physiologic processes (17). An imbalance of the Ca:Mg intake may also lead to

irregularities in many biological activities, such as inflammation, DNA repair, cell proliferation, differentiation, angiogenesis and apoptosis, insulin resistance, and carcinogenesis (22,45). Few in vitro and in vivo studies have evaluated the role of magnesium in carcinogenesis, and the results are inconsistent (45,46). The Ca:Mg intake was not considered in any of these animal studies.

TRPM7 was found to form a functional ion channel complex with TRPM6, contributing essentially to epithelial magnesium (re)absorption (47). Mutations in the *TRPM6* gene were linked to primary hypomagnesemia and secondary hypocalcemia that was due to defects in magnesium absorption (48). Furthermore, TRPM7 deficiency in cells leads to Mg^{2+} deficiency, whereas cellular viability and proliferation can be rescued by extracellular Mg^{2+} but cannot be rescued by Ca^{2+} (23). However, in zebra fish, a developmental defect caused by a mutation in the *TRPM7* gene was partially rescued not only by Mg^{2+}, but also by Ca^{2+} (48), which suggests that TRPM7 may also be involved in regulating the balance of Mg^{2+} and Ca^{2+}. In vitro studies found that heterologously expressed *Thr1482Ile* leads to an elevated sensitivity to inhibition by intracellular Mg^{2+} (24), which suggests that (re)absorption of magnesium is more subject to inhibition among subjects with the *Ile* allele. In the present study, we found that the Thr1482Ile polymorphism significantly interacts with Ca:Mg intake, whereas the associations of magnesium and calcium intakes with the risk of adenoma may differ in persons with ≥1 *1482Ile* allele. These findings are biologically plausible and consistent with previous studies, which suggests that TRPM7 not only possesses a higher affinity for Mg^{2+} than Ca^{2+} (18) but also is involved in magnesium and calcium balance. Moreover, these findings also indicate that, in addition to magnesium or calcium alone, the Ca:Mg intake could provide additional indications for magnesium or calcium status in the body.

The present study has several strengths. Unlike sigmoidoscopy-based studies, the present study included only controls who underwent a full colonoscopy, and, thus, potential contamination of cases in the control group is not a major concern. Moreover, virtually all participants provided a DNA sample. However, the present study also has several limitations. As with all case-control studies, differential recall bias may exist. Yet most participants were recruited before the colonoscopy, and only a few cases were identified as having a malignant lesion; thus, nondifferential recall bias may be minimized. Selection bias is another concern for this case-control study. We have found, however, that age, sex, and the reason for the colonoscopy do not differ between persons who consented and those who did not consent to participate in the study. Furthermore, most participants are recruited before the colonoscopy that defines their case or control status, and, thus, controls are not any less likely to participate than cases. In our study, 55% of all cases underwent colonoscopy as a true screening measure with no indication for the examination other than age. We have conducted analyses of these subjects only and found results that do not differ significantly. Despite this, cautious interpretation of our results is warranted, particularly regarding generalization of our findings. We have used the most common calcium or magnesium ingredients in the calcium and multivitamin supplements to calculate the total intakes of calcium and magnesium. The magnesium content of drinking water could not be included in the calculation of magnesium intake. This may lead to nondifferential misclassification of calcium and magnesium intakes, which usually biases associations toward the null. We have adjusted for many potential confounding factors, but that may not eliminate the possibility that other residual confounding factors, or a related dietary pattern, could explain our results. However, that is unlikely, because, in the present study, the association of magnesium and gene-nutrient interactions was found consistently in both adenomatous and hyperplastic-only cases. Moreover, the association between the functional polymorphism, Thr1482Ile, and the risk of polyps may mimic the link between a low intake of magnesium, a high Ca:Mg intake, or both and polyps. In addition, the association with the polymorphism is not susceptible to confounding according to the Mendelian randomization theory (49), and analyses using genotyping data were conducted among non-

African American subjects only. Of those included in the analyses, 97.4% are white, and Wacholder et al (50) showed that population stratification is not likely to be a serious problem in the white population.

Future studies, including intervention trials, are necessary to confirm our findings. These results, if confirmed, may provide a new avenue for the prevention of magnesium deficiency and, thus, colorectal cancer, particularly in Western populations with a high Ca:Mg intake.

Acknowledgements

We thank the participants and staff of the Tennessee Colorectal Polyp Study. We also thank William Wu, Heidi Chen, and Haojie Wu for assistance with data cleaning; Jirong Long for assistance with the genotyping assay; and Brandy Bentley for editorial assistance. We also appreciate the helpful comments from all of the reviewers.

The authors' responsibilities were as follows—QD and MS: contributed to hypothesis generation, data analysis, result interpretation, and manuscript drafting and revision; MS, RN, WS, and WZ (principal investigator): designed the parent study, implemented and oversaw data collection, assisted in result interpretation, and participated in manuscript revisions; DS: the design of the food-frequency questionnaire, calculation of dietary intakes, and assistance in interpreting results; QC: genotyping assay, interpretation of results, and manuscript revision; and ML and YS: data analysis and manuscript revision. None of the authors had a personal or financial conflict of interest.

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TABLE 1

Comparison of cases and controls by selected descriptive characteristics (Tennessee Colorectal Polyp Study, 2003–2005)[1]

Characteristic	Adenoma cases (n = 688)	Hyperplastic polyp cases (n = 210)	Controls (n = 1306)	P^2	
				Adenoma cases	Hyperplastic polyp cases
Age (y)	59.9 ± 7.2[3]	56.9 ± 6.8	57.7 ± 7.8	<0.01	0.22
Reason for colonoscopy (%)					
Screening	54.9	54.3	55.6		
Family history	9.4	9.5	12.2		
Symptoms	33.7	30.5	29.0	0.05	0.44
Education (%)					
High school or below	34.4	38.8	25.1		
Some college	32.0	28.7	29.7		
College graduates	16.3	15.8	18.7		
Graduate or professional education	17.2	16.7	26.4	<0.01	<0.01
Women (%)	22.2	29.5	42.6	<0.01	<0.01
White (%)	85.5	93.3	88.9	0.12	0.51
Recruitment sites (%)					
Veterans Administration Medical Center	51.2	45.7	34.8		
Vanderbilt Medical Center	48.4	54.3	65.2	<0.01	<0.01
Smoking status (%)					
Never smoker	32.7	26.7	51.4		
Former smoker	38.3	34.3	36.7		
Current smoker	29.0	39.0	11.9	<0.01	<0.01
Alcohol consumption status (%)					
Never drinker	49.3	44.3	59.2		
Former drinker	28.9	31.9	23.1		
Current drinker	21.9	23.8	17.7	<0.01	<0.01
Physically active in the past 10 y (%)	49.6	50	56.7	<0.01	0.14
BMI (kg/m^2)	28.5 ± 5.4	28.4 ± 5.0	27.9 ± 5.5	0.05	0.42
Daily intakes					
Energy (kcal)	1704.9 ± 742.3	1718.0 ± 842.4	1634.5 ± 662.3	0.07	0.34
Folate (μg)	262.6 ± 134.4	265.2 ± 142.1	279.4 ± 128.2	0.01	0.34
Fiber (g)	15.6 ± 7.9	15.6 ± 7.8	16.4 ± 7.5	0.07	0.29
Saturated fat (g)	22.2 ± 11.1	22.6 ± 12.4	20.9 ± 10.3	0.01	0.12
Vitamin E (mg)	7.4 ± 3.4	7.4 ± 3.7	7.4 ± 3.1	1.00	1.00
Vitamin D (IU)	135.9 ± 86.6	137.9 ± 99.9	148.6 ± 90.2	<0.01	0.29
Total calcium (mg)	872.1 ± 466.2	868.7 ± 487.0	981.9 ± 496.6	<0.01	<0.01
Total magnesium (mg)	301.4 ± 128.6	305.1 ± 129.4	321.2 ± 122.1	<0.01	0.16

[1] Nineteen adenoma cases, 4 hyperplastic polyp cases, and 33 controls with unreasonably high or low energy intake were excluded.

[2] Comparisons for both types of cases with controls. The chi-square test (categorical variables) or the t test (continuous variables) was used with Bonferroni adjustment.

[3] $\bar{x}$ ± SD (all such values).

TABLE 2

Odds ratios (and 95% CIs) for colorectal adenoma by tertile (T) of daily magnesium and calcium intake (the Tennessee Colorectal Polyp Study, 2003–2005)[1]

	Intake tertile (mg/d)			
	T1	T2	T3	*P* for trend
Total magnesium intake (mg/d)	≤261	261–368	>368	
Cases/controls (*n*)	276/430	230/429	177/442	
Model 1	1.00[2]	0.82 (0.66, 1.03)[3]	0.60 (0.48, 0.76)	<0.01
Model 2	1.00	0.85 (0.66, 1.11)	0.52 (0.36, 0.76)	<0.01
Model 3	1.00	0.86 (0.66, 1.13)	0.54 (0.36, 0.82)	<0.01
Dietary intake of magnesium (mg/d)	≤211	211–298	>298	
Cases/controls (*n*)	248/431	244/431	196/444	
Model 1	1.00	0.97 (0.77, 1.21)	0.75 (0.60, 0.95)	0.02
Model 2	1.00	1.02 (0.78, 1.35)	0.75 (0.49, 1.15)	0.27
Model 3	1.00	1.05 (0.79, 1.39)	0.80 (0.51, 1.39)	0.42
Total calcium intake (mg/d)	≤ 687	687–1129	>1129	
Cases/controls (*n*)	291/428	219/427	173/439	
Model 1	1.00	0.73 (0.58, 0.91)	0.56 (0.45, 0.71)	<0.01
Model 2	1.00	0.77 (0.60, 1.00)	0.75 (0.55, 1.02)	0.06
Model 3	1.00	0.88 (0.67, 1.16)	0.98 (0.68, 1.40)	0.87
Dietary intake of calcium (mg/d)	≤ 495	495–730	>730	
Cases/controls (*n*)	252/431	215/431	221/444	
Model 1	1.00	0.85 (0.68, 1.07)	0.85 (0.68, 1.07)	0.15
Model 2	1.00	1.00 (0.77, 1.31)	1.01 (0.70, 1.45)	0.97
Model 3	1.00	1.05 (0.80, 1.38)	1.12 (0.76, 1.65)	0.57
Total magnesium intake				
Calcium:magnesium ratio ≤ 2.78				
Cases/controls (*n*)	170/230	135/221	89/203	
Model 1	1.00	0.82 (0.61, 1.10)	0.57 (0.41, 0.79)	<0.01
Model 2	1.00	0.75 (0.53, 1.06)	0.34 (0.20, 0.58)	<0.01
Model 3	1.00	0.78 (0.53, 1.14)	0.38 (0.20, 0.71)	<0.01
Calcium:magnesium ratio > 2.78				
Cases/controls (*n*)	106/200	95/208	88/239	
Model 1	1.00	0.84 (0.59, 1.18)	0.67 (0.48, 0.95)	0.02
Model 2	1.00	0.98 (0.65, 1.49)	0.78 (0.44, 1.40)	0.43
Model 3	1.00	1.02 (0.65, 1.60)	0.85 (0.44, 1.65)	0.66
Total calcium intake				
Calcium:magnesium ratio ≤ 2.78				
Cases/controls (*n*)	246/348	119/254	29/45	
Model 1	1.00	0.65 (0.50, 0.86)	0.87 (0.52, 1.43)	
Model 2	1.00	0.53 (0.37, 0.77)	0.48 (0.22, 1.04)	
Model 3	1.00	0.65 (0.43, 0.99)	0.72 (0.30, 1.69)	
Calcium:magnesium ratio > 2.78				
Cases/controls (*n*)	45/80	100/173	144/394	
Model 1	1.00	0.94 (0.60, 1.48)	0.61 (0.40, 0.92)	
Model 2	1.00	1.11 (0.68, 1.83)	0.97 (0.57, 1.67)	
Model 3	1.00	1.29 (0.76, 2.19)	1.32 (0.69, 2.53)	

[1] Unconditional logistic regression models were used to estimate odds ratio. Model 1 was adjusted for age. Model 2 was also adjusted for educational achievement (categorical); race (white or other); sex; recruitment site; dietary intakes of total energy, saturated fat, folate, vitamin E, retinol equivalent, zinc, vitamin B-6, fiber, and vitamin D; BMI (continuous); physical activity (yes or no); smoking status (former, current, or never); and alcohol consumption status (former, current, or never). Model 3 was also adjusted for total intake of calcium or magnesium. The *P* value for the interaction between the tertiles of total magnesium and calcium intake and the ratio of calcium to magnesium intake (continuous) was 0.10 and 0.24, respectively.

[2] Odds ratio (all such values).

[3] Odds ratio; 95% CIs in parentheses (all such values).

TABLE 3

Odds ratios (ORs) (and 95% CIs) for colorectal adenoma according to the Thr1482Ile polymorphism in the *TRPM7* gene stratified by the ratio of calcium to magnesium intake in non-African American subjects (the Tennessee Colorectal Polyp Study, 2003–2005)[1]

***TRPM7* gene (Thr1482Ile)**	**Cases/controls**	**OR (95% CI)**	***P***
All subjects			
GG	444/907	1.00	
AG/*AA*	137/228	1.20 (0.94–1.53)	
AG	131/214	1.23 (0.96–1.57)	
AA	6/14	0.78 (0.29–2.05)	
P for trend			0.23
Calcium:magnesium intake ratio ≤ 2.78			
GG	259/438	1.00	
AG/*AA*	71/126	0.93 (0.67–1.30)	
AG	69/114	1.00 (0.72–1.41)	
AA	2/12	0.25 (0.05–1.14)	
P for trend			0.36
Calcium:magnesium intake ratio > 2.78			
GG	185/469	1.00	
AG/*AA*	66/102	1.60 (1.12–2.29)	
AG	62/100	1.54 (1.07–2.21)	
AA	4/2	4.45 (0.80–24.80)	
			<0.01
P for interaction			0.03[2]

[1] Unconditional logistic regression models were used to adjust for age.

[2] Thr1482Ile polymorphism × the ratio of calcium to magnesium intake (continuous) interaction.

TABLE 4

Odds ratios (and 95% CIs) for colorectal adenoma according to tertile (T) of magnesium and calcium intakes stratified by the *Thr1482Ile* genotype of the *TRPM7* gene in non-African American subjects (the Tennessee Colorectal Polyp Study, 2003–2005)[1]

***Thr1482Ile* genotype of *TRPM7* gene**	**Intake tertile**			***P* for trend**
	T1 (Low)	**T2**	**T3**	
Total magnesium intake				
All subjects	1.00 (reference)[2]	0.80 (0.60, 1.07)[3]	0.43 (0.28, 0.68)	<0.01
Cases/controls (*n*)	233/374	209/398	156/415	
GG	1.00 (reference)	0.71 (0.51, 1.01)	0.44 (0.26, 0.74)	<0.01
Cases/controls (*n*)	175/277	147/305	120/325	
AG/*AA*	1.00 (reference)	1.11 (0.58, 2.13)	0.20 (0.07, 0.58)	0.02
Cases/controls (*n*)	49/76	57/73	28/78	
Total calcium intake				
All subjects	1.00 (reference)	0.94 (0.71, 1.26)	1.04 (0.71, 1.52)	
Cases/controls (*n*)	244/379	197/390	157/412	
GG	1.00 (reference)	0.80 (0.57, 1.12)	0.93 (0.60, 1.46)	
Cases/controls (*n*)	185/280	139/301	118/323	
AG/*AA*	1.00 (reference)	1.93 (0.99, 3.76)	1.92 (0.79, 4.64)	
Cases/controls (*n*)	47/82	52/72	35/71	

[1] Unconditional logistic regression models were used with adjustment for age; educational level (categorical); race (white or other); sex; recruitment site; dietary intakes of total energy, saturated fat, folate, vitamin E, retinol equivalent, zinc, vitamin B-6, fiber, and vitamin D; BMI (continuous); physical activity (yes or no); smoking status (former, current, or never); alcohol consumption status (former, current, or never); and total intake of calcium or magnesium. The *P* value for the interactions between tertiles of total magnesium and calcium intake and the *Thr1482Ile* genotype was 0.06 and 0.11, respectively.

[2] Odds ratio (all such values).

[3] Odds ratio; 95% CI in parentheses (all such values).

TABLE 5

Odds ratios (and 95% CIs) for hyperplastic polyps by tertile (T) of daily magnesium and calcium intakes in all subjects (the Tennessee Colorectal Polyp Study, 2003–2005)

	Intake tertile			
	T1 (Low)	**T2**	**T3**	***P* for trend**
Total magnesium intake				
All subjects (*n*)	91/430[1]	59/429	59/440	
Model 1[2]	1.00 (reference)[3]	0.65 (0.46, 0.93)[4]	0.64 (0.45, 0.91)	0.01
Model 2[5]	1.00 (reference)	0.73 (0.48, 1.10)	0.60 (0.34, 1.06)	0.07
Model 3[6]	1.00 (reference)	0.75 (0.48, 1.16)	0.64 (0.34, 1.21)	0.15
Total calcium intake				
All subjects (*n*)	86/428	66/427	56/439	
Model 1[2]	1.00 (reference)	0.77 (0.55, 1.09)	0.64 (0.45, 0.92)	0.01
Model 2[5]	1.00 (reference)	0.85 (0.57, 1.28)	0.94 (0.57, 1.53)	0.76
Model 2[6]	1.00 (reference)	0.89 (0.57, 1.38)	1.01 (0.57, 1.79)	0.98

[1] Cases/controls (all such values).

[2] Unconditional logistic regression models were used after adjustment for age.

[3] Odds ratio (all such values).

[4] Odds ratio; 95% CI in parentheses (all such values).

[5] Additionally adjusted for educational achievement (categorical); race (white or other); sex; recruitment site; dietary intakes of total energy, saturated fat, folate, vitamin E, retinol equivalent, zinc, vitamin B-6, fiber, and vitamin D; BMI (continuous); physical activity (yes or no); smoking status (former, current, or never); and alcohol consumption status (former, current, or never).

[6] Further adjusted for total intake of calcium or magnesium.

TABLE 6

Odds ratios for colorectal adenoma according to the Thr1482Ile polymorphism in the *TRPM7* gene among non-African American subjects, stratified by calcium/magnesium intake ratio (the Tennessee Colorectal Polyp Study, 2003–2005)

***TRPM7* genotype (*Thr1482Ile*)**	**Cases/controls**	**OR (95% CI)[1]**	***P***
All subjects			
GG	142/907	1.00	
AG/*AA*	50/228	1.41 (0.99, 2.01)	
AG	45/214	1.35 (0.94, 1.95)	
AA	5/14	2.32 (0.82, 6.55)	
P for trend			0.03
Calcium/magnesium intake ratio ≤ 2.78			
GG	85/438	1.00	
AG/*AA*	27/126	1.12 (0.69, 1.81)	
AG	26/114	1.19 (0.73, 1.94)	
AA	1/12	0.44 (0.06, 3.44)	
P for trend			0.87
Calcium/magnesium intake ratio > 2.78			
GG	57/469	1.00	
AG/*AA*	23/102	1.85 (1.09, 3.14)	
AG	19/100	1.56 (0.89, 2.74)	
AA	4/2	16.14 (2.89, 90.24)	
P for trend			<0.01
P for interaction			0.08[2]

[1] Unconditional logistic regression models were used after adjustment for age.

[2] The *Thr1482Ile* genotype × ratio of calcium to magnesium intake (continuous) interaction.