Research Article

Cancer Epidemiology, Biomarkers & Prevention

Prospective Association of Serum and Dietary Magnesium with Colorectal Cancer Incidence

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Abstract

Background: Laboratory and epidemiologic research suggests a protective role of magnesium in colorectal cancer development. We estimated the associations of serum and dietary magnesium with colorectal cancer incidence in the Atherosclerosis Risk in Communities (ARIC) study.

Methods: Serum magnesium concentration was measured in blood collected twice (1987–1989 and 1990–1992) and averaged. Dietary magnesium was assessed by food-frequency questionnaire administered twice (1987–1989 and 1993–1995) and averaged. For both dietary and serum magnesium, the averaged measures were categorized into quintiles for analysis. Analyses included 315 colorectal cancer cases among 13,009 participants for serum magnesium (followed for a median of 20.4 years), and 256 cases among 10,971 participants for dietary magnesium (followed for a median of 17.5 years). Cox proportional hazards regression was used to calculate multivariable-adjusted HRs and 95% confidence intervals (CI).

Results: Multivariable-adjusted HRs (95% CI) of colorectal cancer for the highest four quintiles compared with the first quintile of serum magnesium were as follows: Q2: 0.70 (0.49–0.99); Q3: 0.68 (0.47–1.00); Q4: 0.87 (0.62–1.21); and Q5: 0.79 (0.57–1.11; $P_{trend} = 0.04$). An inverse association was present in females (HR for Q5 vs. Q1: 0.59, 95% CI: 0.36–0.98, $P_{trend} = 0.01$), but not males (HR for Q5 vs. Q1: 1.10, 95% CI: 0.67–1.79, $P_{trend} = 0.92$; $P_{interaction} = 0.34$). Dietary magnesium was not statistically significantly associated with colorectal cancer risk.

Conclusions: Our study found a higher risk of colorectal cancer with lower serum magnesium among females, but not males.

Impact: If our findings are confirmed, maintaining adequate serum magnesium levels may be important for colorectal cancer prevention.

Introduction

Colorectal cancer is the third most common cancer and the second leading cause of cancer-related death among males and females in the United States (1). Although incidence has decreased over the past several decades, morbidity and mortality remain high, and additional research is needed to understand protective factors for this cancer. The incidence of colorectal cancer has been shown to be lower among those with healthy weight (2) and a diet low in red and processed meats (3) and high in fruits and vegetables (4, 5).

The lower risk of colorectal cancer among those who eat fruits and vegetables may be partially attributed to magnesium. Magnesium is present in many foods that are associated with reduced colorectal cancer incidence, including fruits, vegetables, legumes, and whole grains. However, only 48% of U.S. residents meet United States Department of Agriculture (USDA) dietary recommended daily magnesium intake, which is 400–420 mg/day for adult males and 310–320 mg/day for adult females (6). The average daily magnesium intake in the United States is insufficient for both adult males (347 mg) and females (261 mg; ref. 7).

Magnesium is necessary for intracellular processes that protect against tumor development. Intracellular magnesium modulates enzymatic reactions that maintain DNA stability and repair, such as nucleotide excision repair, base excision repair, and mismatch repair (8). In addition, magnesium deficiency triggers an immune response characterized by increased levels of neutrophils, lymphocytes, and free radicals (8, 9), all of which are hallmarks of inflammatory processes that may contribute to carcinogenesis (8).

Many epidemiologic studies have examined the association between dietary magnesium and the risk of colorectal cancer. A recent meta-analysis of seven prospective cohort studies found significantly lower incidence of colorectal cancer for the highest category of magnesium intake (ranging from 255 to 394 mg/day) compared with the lowest category [ranging from 209 to 278 mg/day; HR: 0.80; 95% confidence interval (CI): 0.73–0.87; ref. 10]. However, because magnesium is present in moderate amounts in a wide variety of healthy foods from disparate food groups, including legumes, milk, meat, and green vegetables, it is difficult to ascertain dietary magnesium intake using self-report methods. A 2011 review of 27 small clinical trials concluded that serum magnesium may be a useful biomarker of magnesium intake,

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Cancer Epidemiol Biomarkers Prev 2019;28:1292–9

doi: 10.1158/1055-9965.EPI-18-1300

because it is responsive to dietary and supplement intake (11). Thus, we estimated the risk of colorectal cancer in relation to serum and dietary magnesium in a population-based prospective cohort of middle-aged black and white males and females, the Atherosclerosis Risk in Communities (ARIC) Study. To our knowledge, no study has examined serum magnesium in association with colorectal cancer incidence.

Methods

Study population

The ARIC study is a prospective cohort study designed to examine the causes and outcomes of atherosclerosis. Since recruitment in 1987–1989, the study has followed males and females between the ages of 45 and 64 years at baseline at four study centers – Forsyth County, NC, Jackson, MS, suburban Minneapolis, MN, and Washington County, MD (12). Participants in Minneapolis and Washington County were primarily white, and participants in Jackson were all black. Data for this analysis were collected at three in-person clinic visits: visit 1, from 1987 to 1989; visit 2, from 1990 to 1992 (the start of follow-up for the main serum magnesium analyses), and visit 3, from 1993 to 1995 (the start of follow-up for the main dietary magnesium analyses). Follow-up via telephone calls has been conducted annually from 1987 to 2012, and semiannually, since 2012. The response rate during follow up was 91% for visit 2 and 81% for visit 3, while the response to phone interviews is 93% (https://www2.cscc.unc.edu/aric/desc_pub). The study protocol was approved by the institutional review board of each participating university and at each visit participants signed their institution's consent form (12).

Assessment of magnesium measures and covariates

Each visit included an examination, during which blood was drawn by trained technicians and stored at −70°C. Blood was collected from participants in the morning after twelve hours of fasting, to control for any diurnal variation. Serum magnesium was measured at visits 1 and 2 (13) as part of the ARIC protocol using the procedure of Gindler and Heth with the metallochromic dye, Calmagite (1-(1-hydroxy-4-methyl-2-phenylazo)-2-napthol-4 sulfonic acid; refs. 13, 14). In samples collected from the same participants 28 days apart, within-person variability was 0.03 SD. In duplicate samples taken simultaneously from the same participants and measured one week apart, measurement-related variability was 0.035 SD (13, 15). The Pearson correlation coefficient between serum magnesium levels at visits 1 and 2 was 0.46. Technicians measured weight and height. For each visit, body mass index (BMI) was calculated as weight (kg) divided by height (in meters) squared.

Participants completed questionnaires and interviews collecting demographic data, social factors, and health behaviors such as physical activity and dietary intake. ARIC participants completed a modified 66-item Harvard Food Frequency Questionnaire (FFQ) at visit 1 and visit 3. In a small reliability study, although dietary magnesium was not assessed, the correlation between self-reported intakes for vitamins and minerals at visit 1 and visit 2 was low ($r = 0.37$–0.49; ref. 16). The Pearson correlation coefficient between the intake of dietary magnesium at visits 1 and 3 was 0.43. Dietary measures for females with caloric intake <500 or >3,500 kcal/day or males <700 or >4,500 kcal/day were considered implausible and excluded. Intake of dietary magnesium and other nutrients, including total calories, calcium, and fiber, was calculated on the basis of reported servings of food intake, and then multiplied by frequency of consumption. Supplemental magnesium intake was not captured.

Physical activity was assessed using a modified version of the Baecke questionnaire from which leisure time physical activity was derived as a function of reported intensity and time spent on sports and exercise. Smoking status was assessed at visits 1, 2, and 3. Pack-years of smoking at visit 1 were derived by multiplying the number of average cigarettes per day times the number of years smoked. Pack-years smoked at visits 2 and 3 were calculated by combining pack-year estimates from visit 1 with smoking status estimates from visits 2 and 3 (e.g., for current smokers at visit 1 and 2, the average time between visits (3 years) was multiplied by the number of daily cigarettes reported at visit 1 and added to visit 1 pack-years).

A participant was considered to have diabetes if s/he had fasting glucose ≥126 mg/dL or nonfasting glucose ≥200 mg/dL or reported that s/he had been diagnosed by a physician or had current treatment for diabetes. Daily alcohol intake was collected at visits 1 and 3 for participants reporting current alcohol intake and calculated as the sum of reported beer, wine, and hard liquor intake.

Assessment of cancer outcome

Incident cancers were ascertained through 2012 via linkage with state cancer registries in Minnesota, North Carolina, Maryland, and Mississippi. These were supplemented by abstraction of medical records and hospital discharge codes (17). Participants who reported a diagnosis of cancer on an annual or semiannual follow-up telephone call were contacted separately for more information on cancer diagnoses, and medical records pertaining to cancer diagnoses and treatment were collected. For reported colorectal cancer cases not previously identified by cancer registries, medical records were abstracted to confirm the diagnosis of cancer. Cancer-related deaths were obtained from death certificates where cancer was listed as the underlying cause of death (17).

Data analysis

Of 15,792 ARIC participants at baseline (visit 1), we excluded from this analysis those who had prevalent cancer at visit 1 ($n = 906$), those who did not give consent for their information to be included in studies on other diseases including cancer or were not able to be linked to cancer registries ($n = 151$), and those with races other than black or white ($n = 48$). Participants missing serum magnesium at visit 1 ($n = 142$) or 2 ($n = 1333$) and those with incident cancer between visits 1 and 2 ($n = 206$) were excluded from the analysis of serum magnesium. Participants with missing or implausible dietary magnesium at visit 1 ($n = 764$) or 3 ($n = 2592$) or incident cancer between visits 1 and 3 ($n = 363$) were excluded from the analysis of dietary magnesium.

Serum magnesium concentration was calculated as the mean of the measurements from visits 1 and 2, and daily dietary magnesium intake was calculated as the mean of the intakes at visits 1 and 3. The mean was used to reflect usual concentration or intake.

Cox proportional hazards regression was used to estimate HRs and 95% CIs for the associations of serum and dietary magnesium with colorectal cancer incidence. Person-years at risk were measured as the time from visit 2 (for serum magnesium) or visit 3 (for dietary magnesium) to first cancer diagnosis, loss of follow-up,

death, or the end of follow-up for this study (December 31, 2012), whichever occurred first.

Cubic splines with five knots at sextiles of serum and dietary magnesium were used to visualize the overall association of magnesium with colorectal risk (Supplementary Figs. S1 and S2). Because splines revealed nonlinear, monotonic associations for both serum and dietary magnesium, both measures were categorized into quintiles in the main analysis. The lowest quintile was a reference in all models. Tests for linear trend were conducted using the median of each category of serum or dietary magnesium. The analysis with dietary magnesium was repeated after dichotomizing magnesium intake based on USDA recommended intake. Participants whose intake was at or above 420 mg/day (for males) or 320 mg/day (for females) (6) were considered to meet recommendations, while those with intake below these cut-off points were not considered to meet recommendations. The proportional hazards assumption was tested by including an interaction term between each magnesium measure and follow-up time in the Cox model. The assumption was not violated for either serum or dietary magnesium measures in any model.

All models were adjusted for age, sex, race, and study center. Because racial groups were distributed unevenly across study centers, a single 4-level variable was created to include a combination of race and study center (white participants from Minnesota, white participants from Maryland and North Carolina, black participants from Mississippi, and black participants from Minnesota, Maryland, and North Carolina). Multivariable-adjusted models additionally included potential confounders identified in previous literature as likely associated with serum or dietary magnesium and with colorectal cancer: total calories (18), BMI (19), physical activity (20, 21), alcohol intake (22, 23), dietary calcium (24, 25), dietary fiber (4), smoking status, pack-years of smoking (26), aspirin use (27), female hormone replacement therapy (HRT) use (28), and diabetes (29–32).

For all analyses, variables that had not changed during the study (race, sex, study center, and education level) were used from visit 1. Variables that could have changed over time were taken as close to the baseline for each measure as possible. Therefore, aspirin use, smoking status and pack-years of smoking, BMI, HRT, age, and diabetes were taken at visit 2 for serum analyses and visit 3 for dietary analyses. Because dietary variables were only available at visits 1 and 3, total energy, calcium, and fiber intakes from visit 1 were used for serum magnesium analyses and dietary measures from visits 1 and 3 were averaged for the dietary magnesium analyses. The variables for smoking status and pack-years were combined and a 10-category variable was created: never smokers; current or former smokers with pack-years of smoking categorized into tertiles, and three separate categories for current, former, and unknown smoking status with missing pack-years. To model female HRT use in the whole sample, a three-category variable was created: female HRT users, female non-HRT users, and males.

When covariate information was missing, values from earlier visits were carried forward, if available. For covariates missing at all visits, missing values were replaced with the mean among participants (for continuous variables) or an additional category for missing data (for categorical variables). Of note, no more than 4% of participants were missing for any variable at all visits.

For both serum and dietary magnesium, we conducted analyses stratified by race and sex. To account for the long latency period of colorectal cancer, we also conducted the analyses stratified by follow-up time at the midpoint (11.5 years for serum analyses and 10 years for dietary analyses). For the analysis of colorectal cancer cases occurring in the first half of follow-up, those with follow-up greater than the midpoint were censored at the midpoint. For the analysis of cancers occurring in the second half of follow-up, person-time accumulated before the midpoint and cancers diagnosed before the midpoint were excluded. We also examined the association with colon and rectal cancers separately for the analysis of serum and dietary magnesium.

Finally, a sensitivity analysis was conducted including all participants for whom magnesium at visit 2 (for serum analyses) or visit 3 (for dietary analyses) was missing, but a baseline measurement was available. As in the main analysis, magnesium from both visits was averaged if available for serum and dietary magnesium. If serum magnesium at visit 2 or dietary magnesium at visit 3 was missing, the measure from baseline was used. Person-years at risk were measured as the time from visit 1 to first cancer diagnosis, loss of follow-up, death, or the end of follow-up for this study, whichever occurred first, for analysis of both serum and dietary magnesium. A two-sided P value of 0.05 was considered statistically significant in all analyses. All analyses were conducted using SAS, version 9.4 (SAS Institute), except cubic spline analysis, which was performed using Stata, version 15. (StataCorp. 2017. Stata Statistical Software: Release 15: StataCorp LLC).

Results

Serum magnesium

As presented in Table 1, among 13,009 participants at baseline, those in higher serum magnesium quintiles were more likely to be male and white, to have higher education and lower BMI. Diabetes was most prevalent in the lowest quintiles of serum magnesium. Dietary magnesium, calcium, and fiber were higher in the higher quintiles of serum magnesium. Most participants (88%) fell within recommended serum magnesium levels (1.4–1.8 mEq/L).

During 222,202 person-years of follow-up, 315 incident colorectal cancer cases were identified, including 271 colon and 45 rectal cancers. After adjusting for age, race, center, and sex (Table 2), HRs (95% CI) of colorectal cancer for each quintile compared with the first quintile of serum magnesium were: Q2: 0.66 (0.47–0.93); Q3: 0.64 (0.44–0.93) Q4: 0.82 (0.59–1.13); and Q5: 0.79 (0.57–1.11); $P_{trend} = 0.01$. The association remained statistically significant after further adjustment for total calories, dietary calcium, dietary fiber, BMI, physical activity, alcohol intake, smoking status, pack-years of smoking, aspirin use, female HRT use, and diabetes, with a P_{trend} of 0.04 (Table 2). There was an indication of inverse association for both colon (HR for Q5 vs. Q1: 0.84, 95% CI: 0.58–1.23, $P_{trend} = 0.25$) and rectal cancer (HR for Q5 vs. Q1: 0.48, 95% CI: 0.21–1.16, $P_{trend} = 0.01$, $P_{interaction} > 0.99$; Supplementary Table S1). Similar inverse associations were observed between serum magnesium and colorectal cancer in a sensitivity analysis with follow-up started at visit 1 (Supplementary Table S2).

Table 3 presents the analysis stratified by sex ($P_{interaction} = 0.34$) and race ($P_{interaction} = 0.74$). Inverse associations were observed among females (HR for Q5 vs. Q1: 0.59, 95% CI: 0.36–0.98,

Table 1. Characteristics of participants by serum magnesium quintiles (ARIC 1987–1992)

	Serum magnesium quintiles[a] (mEq/L)				
Participant characteristics	**0.60–1.50**	**1.51–1.59**	**1.60–1.65**	**1.66–1.70**	**1.71–2.65**
N	2,829	2,650	2,058	2,649	2,823
Dietary magnesium intake (mg/day)[b,c]	247 (95)	253 (95)	255 (95)	255 (92)	263 (98)
Age in years[c,d]	56.9 (5.8)	56.7 (5.8)	56.9 (5.6)	56.9 (5.6)	57.2 (5.7)
Male sex[b,e]	1,160 (41)	1,147 (43)	960 (47)	1,298 (49)	1,358 (48)
Black race[b,e]	1,200 (42)	681 (26)	440 (21)	496 (19)	439 (16)
Educational attainment (>high school)[b,e]	1,986 (70)	2,068 (78)	1,631 (79)	2,162 (82)	2,280 (81)
Use of aspirin in the preceding 2 weeks[d,e]	1,417 (50)	1,316 (50)	1,068 (52)	1,319 (50)	1,575 (52)
Current smoker[d,e]	691 (25)	584 (22)	451 (22)	580 (22)	608 (22)
Diabetes[d,e]	646 (23)	282 (11)	159 (8)	191 (7)	124 (4)
HRT use (females only)[d,e]	746 (45)	684 (46)	497 (46)	594 (44)	633 (4)
Physical activity index[b,c]	2.3 (0.8)	2.4 (0.8)	2.4 (0.8)	2.5 (0.8)	2.5 (0.8)
Alcohol intake (grams/d)[b,c]	6.0 (15.5)	5.4 (12.4)	6.5 (13.2)	6.2 (12.6)	6.5 (12.7)
BMI (kg/m^2)[c,d]	29.3 (6.2)	28.1 (5.5)	27.8 (5.1)	27.5 (5.1)	27.2 (4.6)
Energy intake (kcal/day)[b,c]	1626 (734)	1634 (692)	1627 (656)	1629 (658)	1656 (697)
Dietary calcium intake (mmol/L)[b,c]	634 (376)	653 (379)	661 (379)	662 (364)	679 (394)
Dietary fiber intake (g/day)[b,c]	17.0 (8.3)	17.4 (8.0)	17.2 (8.1)	17.2 (7.8)	17.6 (8.6)

[a]Average of characteristics assessed at visits 1 (1987–1989) and 2 (1990–1992).
[b]Characteristics assessed at visit 1 (1987–1989).
[c]Mean (SD).
[d]Characteristics assessed at visit 2 (1990–1992).
[e]Number (%).

$P_{trend} = 0.01$) and white participants (HR for Q5 vs. Q1: 0.70, 95% CI: 0.47–1.04, $P_{trend} = 0.02$), whereas no association was observed in men (HR for Q5 vs. Q1: 1.10, 95% CI: 0.67–1.79, $P_{trend} = 0.92$) or black participants (HR for Q5 vs. Q1: 0.93, 95% CI: 0.46–1.89, $P_{trend} = 0.77$). The HRs for colorectal cancer were similar for follow-up $\leq$ 11.5 years (HR for Q5 vs. Q1: 0.71, 95% CI: 0.44–1.14, $P_{trend} = 0.15$) or >11.5 years (HR for Q5 vs. Q1: 0.85, 95% CI: 0.53–1.37, $P_{trend} = 0.14$; Supplementary Table S3).

Table 2. HR and 95% CIs for the association between serum magnesium quintiles and colorectal cancer risk[a] (ARIC 1990–2012)

Serum magnesium quintiles (mEq/L)	**0.60–1.50**	**1.51–1.59**	**1.60–1.65**	**1.66–1.70**	**1.71–2.65**	**P_{trend}**
Number of cases	83	54	42	70	66	
Person-years	45,765	45,472	35,571	46,451	48,943	
HR (95% CI)[b]	1 (ref)	0.66 (0.47–0.93)	0.64 (0.44–0.93)	0.82 (0.59–1.13)	0.72 (0.52–1.01)	0.01
HR (95% CI)[c]	1 (ref)	0.70 (0.49–0.99)	0.68 (0.47–1.00)	0.87 (0.62–1.21)	0.79 (0.57–1.11)	0.04

[a]Follow-up beginning at visit 2 (1990–1992). Serum magnesium assessed as the average of visits 1 (1987–1989) and 2 (1990–1992).
[b]Model adjusted for age, sex, race, and study center.
[c]Model noted in footnote b further adjusted for total calories, dietary calcium, dietary fiber, BMI, physical activity, alcohol intake, smoking status, pack-years of smoking, aspirin use, HRT use, and diabetes.

Table 3. HR and 95% CIs for the association between serum magnesium and colorectal cancer risk, by sex and race[a] (ARIC 1990–2012)

Serum magnesium quintiles (mEq/L)	**0.60–1.50**	**1.51–1.59**	**1.60–1.65**	**1.66–1.70**	**1.71–2.65**	**P_{trend}**
Sex ($P_{interaction}$: 0.34)						
Males						
Number of cases	32	31	21	40	41	
Person-years	17,048	18,392	15,647	21,450	22,443	
HR (95% CI)[b]	1 (ref)	0.98 (0.59–1.62)	0.78 (0.45–1.38)	1.07 (0.66–1.74)	1.10 (0.67–1.79)	0.92
Females						
Number of cases	51	23	21	30	25	
Person-years	28,717	27,081	19,923	25,001	26,500	
HR (95% CI)[b]	1.00 (ref.)	0.54 (0.33–0.89)	0.65 (0.39–1.10)	0.78 (0.48–1.25)	0.59 (0.36–0.98)	0.01
Race ($P_{interaction}$: 0.74)						
White participants						
Number of cases	52	37	31	57	54	
Person-years	26,877	34,095	28,211	37,799	41,565	
HR (95% CI)[c]	1 (ref)	0.60 (0.39–0.93)	0.59 (0.38–0.93)	0.80 (0.55–1.19)	0.70 (0.47–1.04)	0.02
Black participants						
Number of cases	31	17	11	13	12	
Person-years	18,887	11,378	7,360	8,652	7,378	
HR (95% CI)[c]	1 (ref)	0.91 (0.50–1.66)	0.96 (0.48–1.94)	0.93 (0.48–1.79)	0.93 (0.46–1.89)	0.77

[a]Follow-up beginning atvisit 2 (1990–1992). Serum magnesium assessed as the average of visits 1 (1987–1989) and 2 (1990–1992).
[b]Model adjusted for age, race, study center, total calories, dietary calcium, dietary fiber, BMI, physical activity, alcohol intake, smoking status, pack-years of smoking, aspirin use, HRT use, and diabetes.
[c]Model adjusted for age, sex, study center, total calories, dietary calcium, dietary fiber, BMI, physical activity, alcohol intake, smoking status, pack-years of smoking, aspirin use, HRT use, and diabetes.

Dietary magnesium

The analytic dataset for the assessment of dietary magnesium included 10,971 participants. Participants in the higher quintiles of magnesium intake were more likely to be male, white, and have at least high school education. Those with higher dietary magnesium were more likely to smoke and less likely to use HRT (among females), and reported higher alcohol, caloric, dietary calcium, and dietary fiber intake than those in the lower quintiles (Supplementary Table S4).

Between 1993 and 2012, 256 cases of incident colorectal cancer, including 220 colon and 36 rectal cancers, were identified over 163,130 person-years. After adjusting for age, race, sex, and center, total calories, dietary calcium, dietary fiber, BMI, physical activity, alcohol intake, smoking status, pack-years of smoking, aspirin use, female HRT, and diabetes, there was no statistically significant association between quintiles of dietary magnesium and colorectal cancer risk. HRs (95% CIs) were: Q2: 1.13 (0.74–1.71); Q3: 0.85 (0.53–1.37); Q4: 0.91 (0.54–1.54); and Q5: 0.77 (0.38–1.55), $P_{trend} = 0.61$ (Table 4). In the analysis stratified by site, there was no association between dietary magnesium quintiles and colon ($P_{trend} = 0.41$) or rectal ($P_{trend} = 0.45$) cancers (Supplementary Table S5). Similarly, no associations were observed in two sensitivity analyses assessing the association between colorectal cancer and (i) quantiles of dietary magnesium with follow-up beginning at visit 1 (Supplementary Table S6) or (ii) magnesium intake dichotomized at USDA dietary magnesium recommendations (Supplementary Table S7).

No associations were observed between dietary magnesium and colorectal cancer among women (HR for Q5 vs. Q1: 0.51, 95% CI: 0.17–1.54, *p*-trend = 0.43) or men (HR for Q5 vs. Q1: 1.09, 95% CI: 0.42–2.83, *p*-trend = 0.91), but there was evidence for interaction by sex (*p*-interaction = 0.04) (Table 5). There were no significant associations in analyses stratified by race (*p*-interaction = 0.13) (Table 5). Likewise, dietary magnesium was not associated with colorectal cancer in analyses before or after the midpoint of the period of follow-up (Supplementary Table S8).

Discussion

In this analysis of serum magnesium and colorectal cancer risk in the ARIC cohort, we found evidence of an inverse association: those in the highest quintile of serum magnesium had 21% lower risk of colorectal cancer compared with those in the first quintile. However, the HRs for colorectal cancer were lowest in the second and third quintiles (ranging from 1.50–1.65 mEq/L), suggesting that the association between serum magnesium and colorectal cancer may be U-shaped, rather than linear. Among females, the inverse association between serum magnesium and colorectal cancer risk was stronger and statistically significant, while no association was observed in males. We observed no association between dietary magnesium and colorectal cancer risk.

The inverse association between magnesium and colorectal cancer risk has a strong biological rationale. Magnesium is necessary for multiple processes including DNA replication, repair, gene expression, and apoptosis, as well as maintaining DNA stability (33). Laboratory studies in animals have shown that, when DNA is damaged, magnesium is essential for catalyzing enzymatic reactions at each step of repair (33–35). In addition, studies in rats have found that magnesium supplementation inhibits the effects of carcinogens (34).

While, to our knowledge, this is the first study to investigate the association between serum magnesium and colorectal cancer risk, one previous study has examined cancer incidence in relation to serum magnesium. A cross-sectional study of 494 participants including 98 high-grade prostate cancer cases, found a significant inverse association of high-grade prostate cancer incidence for the highest category of serum magnesium versus the lowest (OR: 0.26, 95% CI, 0.24–0.96; ref. 36).

Although research on serum magnesium and cancer is limited, the association between dietary magnesium and colorectal cancer risk has been examined in multiple studies. Four meta-analyses of prospective studies of dietary magnesium reported statistically significant inverse associations with colorectal cancer risk ranging from 0.80 to 0.89 for the highest category of dietary magnesium (ranging from 255–394 mg/day) compared with the lowest (ranging from 209–278 mg/day; refs. 10, 37–40). However, similar to our study findings, five cohort studies included in those meta-analyses also reported no association between dietary magnesium and colorectal cancer (41–45).

Our findings indicate an inverse association of serum magnesium with colorectal cancer risk among female, but not male participants. Meta-analyses of prospective studies of dietary magnesium support an inverse association between magnesium and colorectal cancer risk among women but not men (40), although five of nine studies included in those meta-analyses were conducted in women only. Furthermore, an inverse association with serum magnesium was observed among white, but not black participants, but estimates were imprecise, especially for black participants. Further prospective studies of multiracial cohorts are needed to determine and explain whether the associations between serum and dietary magnesium and colorectal cancer differs by sex or race.

In addition, we observed a stronger association of serum magnesium with rectal cancer than with colon cancer. This association was not observed in our analysis of dietary magnesium, while meta-analyses of prospective studies have found significant associations of dietary magnesium with colon, but not rectal cancer (10). Serum magnesium has not previously been studied in relation to colon or rectal cancer, and further research is needed to confirm or refute the stronger association of serum magnesium with rectal than colon cancer observed here.

Misclassification of dietary magnesium may explain the lack of association with colorectal cancer risk in our study despite using

Table 4. HR and 95% CI for the association between dietary magnesium quintiles and colorectal cancer risk[a] (ARIC 1993–2012)

Dietary magnesium (mg/day)	58.68–185.35	185.36–226.07	226.08–265.62	265.64–318.73	318.79–792.01	P_{trend}
Number of cases	46	57	47	53	53	
Person-years	32,793	32,666	32,940	32,992	31,739	
HR (95% CI)[b]	1 (ref)	1.19 (0.81–1.75)	0.97 (0.64–1.46)	1.08 (0.73–1.61)	1.12 (0.75–1.67)	0.63
HR (95% CI)[c]	1 (ref)	1.13 (0.74–1.71)	0.85 (0.53–1.37)	0.91 (0.54–1.54)	0.77 (0.38–1.55)	0.61

[a]Follow-up beginning at visit 3 (1993–1995). Dietary magnesium assessed as the average of visits 1 (1987–1989) and 3 (1993–1995).
[b]Model adjusted for age, sex, race, and study center.
[c]Model noted in footnote b further adjusted for total calories, dietary calcium, dietary fiber, BMI, physical activity, alcohol intake, smoking status, pack-years of smoking, aspirin use, HRT use, and diabetes.

Table 5. HR and 95% CI for the association between dietary magnesium and colorectal cancer risk, by sex and race[a] (ARIC 1993–2012)

Dietary magnesium quintiles (mEq/L)	58.68–185.35	185.36–226.07	226.08–265.62	265.64–318.73	318.79–792.01	P_{trend}
Sex ($P_{interaction}$: 0.04)						
Males						
Number of cases	16	31	16	30	38	
Person-years	9,639	12,056	13,872	15,516	16,809	
HR (95% CI)[b]	1 (ref)	1.67 (0.87–3.20)	0.65 (0.30–1.41)	1.11 (0.52–2.39)	1.10 (0.43–2.87)	0.88
Females						
Number of cases	30	26	31	23	15	
Person-years	23,154	20,610	19,068	17,476	14,930	
HR (95% CI)[b]	1.00 (ref.)	0.88 (0.50–1.55)	1.09 (0.58–2.04)	0.79 (0.36–1.72)	0.51 (0.17–1.54)	0.43
Race ($P_{interaction}$: 0.13)						
White participants						
Number of cases	30	47	31	36	45	
Person-years	23,548	25,157	26,166	26,365	25,864	
HR (95% CI)[c]	1 (ref)	1.31 (0.81–2.13)	0.79 (0.45–1.39)	0.87 (0.47–1.60)	0.91 (0.42–2.00)	0.79
Black participants						
Number of cases	16	10	16	17	8	
Person-years	9,244	7,509	6,774	6,627	5,876	
HR (95% CI)[c]	1 (ref)	0.63 (0.27–1.49)	0.96 (0.39–2.35)	0.95 (0.34–2.65)	0.36 (0.07–1.82)	0.40

[a]Follow-up beginning at visit 3 (1993–1995). Dietary magnesium assessed as the average of visits 1 (1987–1989) and 3 (1993–1995).
[b]Adjusted for age, race, study center, total calories, dietary calcium, dietary fiber, BMI, physical activity, alcohol intake, smoking status, pack-years of smoking, aspirin use, HRT use, and diabetes.
[c]Adjusted for age, sex, study center, total calories, dietary calcium, dietary fiber, BMI, physical activity, alcohol intake, smoking status, pack-years of smoking, aspirin use, HRT use, and diabetes.

the mean of two time points. Magnesium is present in moderate amounts in many foods, so it is difficult to capture its intake using self-reported FFQs (16), although a Swedish study of 61,433 women that used 60-item FFQ similar to the one used in this study found an inverse association (46). Although the within-person correlation for questionnaires provided one year apart in the standard 61-item Harvard FFQ was reasonable (coefficients of correlation were 0.63 for total calories and 0.64 for dietary fiber; ref. 47); the reproducibility of magnesium intake has not been reported. Furthermore, our study did not capture supplemental magnesium intake, leading to potential misclassification of dietary intake and attenuation of the association with colorectal cancer.

In addition, it is likely that magnesium measures and other covariates varied in over 20 years of follow-up. However, in analyses of both serum and dietary magnesium, HRs were similar for cases of colorectal cancer occurring before and after the midpoint of follow-up of 11.5 years for serum magnesium and 10 years for dietary magnesium analyses. Unfortunately, neither serum nor dietary magnesium has been measured after visits 2 and 3, respectively, in the ARIC study.

As in all observational studies, although we adjusted for potential confounders, residual confounding by strong confounders may partially explain the observed associations between serum magnesium and colorectal cancer. For instance, individuals with diabetes or alcohol users have lower levels of magnesium (15, 30, 48, 49) and may also have higher risk of colorectal cancer (23, 29, 31); therefore, it is possible that adjustment for those factors did not completely remove their confounding effect. Furthermore, we have included diabetes in our multivariable models as a confounder. However, the association between magnesium and diabetes may be bidirectional. While diabetes has been shown to initiate hypomagnesemia in laboratory studies (50), epidemiologic studies indicate that low serum and dietary magnesium are prospectively associated with diabetes (51). If diabetes is a mediator of this association, the total inverse association between magnesium and colorectal cancer risk could be even stronger than the association reported in this study.

An additional limitation is that low reported dietary intake in our study may impact the generalizability of our findings. Only 12% of our participants report magnesium intake meeting current dietary USDA recommendations, compared with 48% of U.S. residents in a 2009 population-based survey (7). However, the magnesium intakes are comparable with intakes reported in the United States in the late 1980s when the ARIC study was initiated. Mean dietary magnesium in our sample was 255 mg/day, compared with 236 mg/day in the United States population in 1987–1988 (52), suggesting that our findings reflect typical dietary patterns at the time.

It is not clear to what extent serum magnesium is modifiable by dietary consumption. A recent meta-analysis of 48 small clinical trials (total $n = 2131$) reported that serum magnesium was responsive to dietary supplementation (53). Although these findings suggest that serum magnesium may estimate dietary intake, serum magnesium is highly regulated and poorly correlated with dietary magnesium in observational studies, although poor correlation may be partially explained by inaccurate assessment of dietary magnesium intake. For instance, in our study, the coefficient of correlation between serum and dietary magnesium was $r = 0.02$ ($P = 0.01$). Serum magnesium makes up a small proportion of total magnesium in the body and cannot serve as a good biomarker for total magnesium status or intracellular magnesium. Despite these limitations, serum magnesium is used in clinical practice, because no better measures of magnesium in the body are known. Thus, although these results should be interpreted with caution, the previous research on dietary magnesium and colorectal cancer together with our findings on serum magnesium suggest an inverse association between magnesium and colorectal cancer risk.

With 13,009 participants and 23 years of prospective follow-up, this study has several important strengths. Serum and dietary magnesium were each assessed at two time points and averaged, allowing for more precise measurement of usual concentration or intake in our study. In addition, cancer cases were reliably ascertained via linkage to state cancer registries and supplemented by hospital records (17), and information about multiple

confounders was collected. Although additional studies are needed to corroborate our findings with more sensitive measures of magnesium status, this study confirmed our hypothesis and provided the first evidence of an inverse association between serum magnesium and colorectal cancer risk.

Disclosure of Potential Conflicts of Interest

The Editor-in-Chief of Cancer Epidemiology, Biomarkers & Prevention is an author on this article. In keeping with AACR editorial policy, a senior member of the Cancer Epidemiology, Biomarkers & Prevention editorial team managed the consideration process for this submission and independently rendered the final decision concerning acceptability.

Disclaimer

The content of this work is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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Acknowledgments

Cancer incidence data have been provided by Maryland Cancer Registry, Center of Cancer Surveillance and Control, Maryland Department of Health (201 West Preston Street, Room 400, Baltimore, MD 21201). The authors acknowledge the State of Maryland, the Maryland Cigarette Restitution Fund, and the National Program of Cancer Registries of the CDC for the funds that helped support the availability of the cancer registry data. The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, NIH, Department of Health and Human Services, under contract numbers listed as follows: HHSN2682017000001I (to D.J. Couper), HHSN2682017000002I (to J. Coresh), HHSN2682017000003I (to A. Folsom), HHSN2682017000005I (to G. Heiss), and HHSN2682017000004I (to T.H. Mosley). The authors thank the staff and participants of the ARIC study for their important contributions. Studies on cancer in ARIC are also supported by the National Cancer Institute (U01 CA164975, to E.A. Platz). This work was additionally supported by P30 CA006973 (to W. Nelson).

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Received December 2, 2018; revised February 18, 2019; accepted May 31, 2019; published first June 5, 2019.

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