Null Results in Brief

Total Magnesium Intake and Colorectal Cancer Incidence in Women

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Introduction

Magnesium is an essential ion that has an important role in regulating cell cycles and maintaining genomic stability (1). Administration of supplemental magnesium in animals with experimentally induced colon cancer resulted in fewer colon tumors and smaller cryptal cells of the colon (2), suggesting an inhibitory role of magnesium in colon cancer cell proliferation. The mechanism by which magnesium prevents the growth of colon tumors was later found to be due to the inhibition of c-*myc* oncogene expression in the colon cancer cells (3) and the potentially reduced toxic effects of bile acids on colonic epithelial cells (4). At the intracellular level, magnesium also effectively modulates insulin activity (5, 6). Magnesium deficiency is often seen among patients with insulin resistance and type 2 diabetes (5, 6), which have also been linked to an increase in colorectal cancer incidence (7-9).

Observational studies of the association between magnesium intake and colorectal cancer incidence are very sparse. A case-control study found that magnesium level in drinking water was not associated with death from cancers of the colon (10) and rectum (11). On the basis of a dietary questionnaire, however, two recent prospective studies observed an inverse association between total magnesium intake and incident colorectal cancer (12, 13), although one study reported that the inverse association was only limited to colon cancer (13). Because more data are needed to confirm the association, we prospectively evaluated the association between total magnesium intake and colorectal cancer incidence in middle-aged and older women in the Women's Health Study.

Materials and Methods

The Women's Health Study is a completed randomized trial evaluating low-dose aspirin and vitamin E for the primary prevention of cancer and cardiovascular disease among 39,876 female health professionals who were 45 years or older and were free of cancer at the time of enrollment beginning in 1993 (14-16). At baseline, participants completed a questionnaire about their medical history and potential risk factors for colorectal cancer. Participants were also asked to fill out a 131-item food frequency questionnaire, which asked the average intake of foods and beverage during the past year. Nine responses were available, ranging from ''never or less than once per month'' to ''six or more times per day.'' Participants also reported the brand and type of multivitamins they used and how many times they took multivitamins per week, which were then used to estimate supplemental magnesium intake. Individual nutrient intake was calculated by multiplying the frequency of intake by the nutrient content of the specified portion size. Nutrient intakes were also energy adjusted based on the residual methods (17). Total intake of magnesium was estimated from both dietary and supplemental sources. The reproducibility and validity of total magnesium intake have been assessed in the Nurses Health Study; the Pearson correlation coefficient between total magnesium intake by the food frequency questionnaire and two 1-week diet records was 0.76 (18, 19). In the present study, we excluded women for whom we had no information on magnesium intake and for whom information on potential risk factors for colorectal cancer was not available. This left a total of 38,345 women for the present analysis.

We first categorized women into quintiles according to intake of total magnesium and compared the baseline distribution of risk factors for colorectal cancer according to these quintiles. Cox proportional hazards regression was then used to estimate the relative risk (RR) and 95% confidence interval (95% CI) with adjustment for age and random treatment assignment, and additionally for risk factors for colorectal cancer. Tests for trend were done by fitting the median of nutrient intake for each quintile as a continuous variable in the models. All P values were two sided.

Results

During an average of 11 years of follow-up, 259 women had a confirmed diagnosis of colorectal cancer. The average intake of total magnesium in this cohort was 338 $\pm$ 74 (SD) mg/d. The mean values for intake from dietary and supplemental sources were 323 and 14 mg/d, respectively. Women who consumed more magnesium tended to be older and leaner (Table 1). Women reporting higher intake of magnesium were also more likely to have healthy lifestyle habits; they were more likely to receive colorectal screening tests, be more physically active, and be current users of postmenopausal hormone therapy and multivitamin supplements. In addition,

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they were less likely to be current smokers; consumed less alcohol, saturated fat, and red meat; and had higher intakes of calcium, fiber, zinc, vitamin E, β-carotene, folate, and vitamin B_6.

Total intake of magnesium was not associated with colorectal cancer incidence in models adjusted for age and randomized treatment and additionally for other risk factors for colorectal cancer (Table 2). When compared with those in the lowest quintile of total magnesium intake, women in the highest quintile had a multivariate RR of 0.97 (95% CI, 0.63-1.49) for colorectal cancer incidence (P_{trend} = 0.88). The results were not materially changed when we additionally adjusted, one at a time or simultaneously, for intakes of saturated fat, fiber, calcium, zinc, vitamin E, β-carotene, folate, and vitamin B_6 (data not shown). Intake of magnesium from dietary sources was also not associated with colorectal cancer incidence (Table 2). When we repeated the analysis of magnesium intake from diet by excluding supplement users, the results were not appreciably changed (P_{trend} = 0.84).

Higher intakes of total and dietary magnesium were not significantly associated with a lower risk of cancers of the colon and rectum (Table 2). However, there was a nonsignificantly inverse association between total and dietary magnesium intake and risk of rectal cancer; women in the highest quintile had multivariate RRs of 0.65 (95% CI, 0.24-1.78) for total magnesium and 0.78 (95% CI, 0.31-1.92) for dietary magnesium in comparison with those in the lowest quintile. Intake of supplemental magnesium was very low in this cohort to allow for meaningful tests.

Potential confounding factors, including body mass index, physical activity, smoking status, and current use of postmenopausal hormone therapy, did not modify the association between total magnesium intake and colorectal cancer incidence (multivariate P values for interactions >0.24). The results were also unchanged according to history of diabetes at baseline (multivariate P_{trend} = 0.55) and when stratified by colonoscopy or sigmoidoscopy screening tests (multivariate P_{trend} = 0.67).

Discussion

In this prospective cohort of women, we observed no significant association between intake of total magnesium and colorectal cancer incidence. Intake of magnesium from dietary sources was also not significantly associated with colorectal cancer incidence. In addition, the associations were not modified according to tumor location and by several potential risk factors for colorectal cancer.

Very few observational studies have evaluated the association between magnesium intake and colorectal cancer risk. Our finding of a null association between total magnesium intake and colorectal cancer incidence is in agreement with an Asian case-control study, which observed no association between magnesium intake in drinking water and death from cancers of the colon (10) and rectum (11). However, both the Swedish cohort study and the Iowa Women's Health Study reported an inverse association between total magnesium intake and colon cancer risk (12, 13), with the Swedish cohort study also reporting an inverse association with rectal cancer risk (12). One possible explanation for the different findings among these cohorts is that high magnesium intake may be related to a reduced risk of colorectal cancer only among populations with relatively low intake levels of magnesium. In this cohort, the median intake of total magnesium was much greater (329 mg/d) compared with that in the other two cohorts (232 and 302 mg/d, respectively; refs. 12, 13). Accordingly, the majority of women in this cohort who have sufficient intake of magnesium may be able to receive only minimal benefit. It is also possible that obesity may have contributed to the different findings, as most women in the Swedish cohort had normal body mass index (i.e., <25 kg/m^2), and our group have previously reported that the inverse association between total magnesium intake and type 2 diabetes incidence was more apparent among overweight and obese women (20). However, this explanation is not supported by our analyses stratified by body mass index, which show no appreciable differences. Because serum magnesium is not well correlated with dietary intake (21), it

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Table 1. Age-adjusted baseline characteristics according to total intake of energy-adjusted magnesium in the Women's Health Study

	Total magnesim intake (mg/d)					
	Q1*	Q2	Q3	Q4	Q5	P_{trend}
Median intake value	255	296	329	365	433	
Participants	7,691	7,691	7,693	7,690	7,690	
Age (y)	52.6	53.3	53.9	54.5	55.3	<0.0001
Body mass index (kg/m^2)	26.7	26.3	26.0	25.7	25.3	<0.0001
Family history of colorectal cancer (%)	10.8	10.1	10.3	10.1	10.3	0.66
Screening test of colonoscopy or sigmoidoscopy (%) †	6.2	6.9	7.5	7.3	8.4	<0.0001
Colorectal polyps (%)	2.8	2.7	2.3	2.2	2.5	0.06
Postmenopausal HT (% current use)	38.3	41.0	42.9	43.4	44.6	<0.0001
Multivitamin use (% current use)	17.2	20.5	23.7	31.0	54.4	<0.0001
Physical activity (kcal/wk)	650	829	964	1,129	1,283	<0.0001
Current cigarette smoking (%)	17.2	14.7	13.0	10.8	9.5	<0.0001
Alcohol consumption (g/d)	4.3	4.4	4.3	4.1	3.6	<0.0001
Red meat intake (serving/d)	0.9	0.8	0.7	0.6	0.5	<0.0001
Total calories intake (kcal/d)	1,677	1,735	1,765	1,766	1,687	<0.0001
Saturated fat intake (g/d) ‡	22.4	21.0	19.7	18.4	16.9	<0.0001
Total fiber intake (g/d) ‡	14	17	19	21	24	<0.0001
Total calcium intake (mg/d) ‡	765	899	999	1,105	1,300	<0.0001
Total zinc intake (g/d) ‡	11	12	13	15	22	<0.0001
Total vitamin E intake (mg/d) ‡	54	56	59	69	95	<0.0001
Total β-carotene intake (μg/d) ‡	3,127	3,960	4,647	5,396	6,892	<0.0001
Total folate intake (μg/d) ‡	305	361	399	457	622	<0.0001
Total vitamin B_6 intake (mg/d) ‡	3	4	5	6	8	<0.0001

Abbreviation: HT, hormone therapy.
*Q, quintile.
†From the 12-month questionnaire.
‡Energy-adjusted values.

Table 2. RRs and 95% CIs of colorectal cancer according to quintile intakes of energy-adjusted magnesium in the Women Health's Study

	Quintile intake					P_{trend}
	1	2	3	4	5	
Total magnesium*						
Intake (mg/d)	<279	279 to <313	313 to <346	346 to <392	≥392	
Colorectal cancer						
No. cases	48	48	40	61	62	
RR (95% CI) †	1.00	0.92 (0.62-1.38)	0.73 (0.48-1.11)	1.06 (0.72-1.54)	0.99 (0.68-1.45)	0.68
RR (95% CI) ‡	1.00	0.99 (0.65-1.49)	0.77 (0.49-1.18)	1.11 (0.74-1.66)	0.97 (0.63-1.49)	0.89
Colon cancer						
No. cases§	36	34	33	45	51	
RR (95% CI) †	1.00	0.87 (0.54-1.39)	0.79 (0.49-1.27)	1.03 (0.66-1.60)	1.08 (0.70-1.66)	0.42
RR (95% CI) ‡	1.00	0.93 (0.57-1.50)	0.85 (0.52-1.40)	1.11 (0.70-1.77)	1.04 (0.64-1.69)	0.64
Rectal cancer						
No. cases§	11	14	7	13	8	
RR (95% CI) †	1.00	1.21 (0.55-2.67)	0.59 (0.23-1.52)	1.05 (0.47-2.36)	0.62 (0.25-1.55)	0.27
RR (95% CI) ‡	1.00	1.31 (0.58-2.96)	0.60 (0.23-1.61)	1.05 (0.44-2.49)	0.65 (0.24-1.78)	0.32
Magnesium from diet*						
Intake (mg/d)	<275	275 to <306	306 to <334	334 to <369	≥369	
Colorectal cancer						
No. cases	51	50	49	45	64	
RR (95% CI) †	1.00	0.91 (0.62-1.34)	0.84 (0.57-1.24)	0.73 (0.49-1.09)	0.96 (0.66-1.40)	0.71
RR (95% CI) ‡	1.00	0.99 (0.67-1.48)	0.87 (0.58-1.32)	0.77 (0.50-1.18)	0.95 (0.63-1.44)	0.62
Colon cancer						
No. cases§	38	36	41	35	49	
RR (95% CI) †	1.00	0.88 (0.56-1.38)	0.93 (0.60-1.45)	0.76 (0.48-1.20)	0.98 (0.64-1.49)	0.84
RR (95% CI) ‡	1.00	0.97 (0.61-1.55)	0.99 (0.62-1.58)	0.81 (0.50-1.32)	0.97 (0.60-1.57)	0.77
Rectal cancer						
No. cases§	12	14	8	8	11	
RR (95% CI) †	1.00	1.11 (0.51-2.40)	0.61 (0.25-1.50)	0.60 (0.24-1.46)	0.78 (0.34-1.78)	0.30
RR (95% CI) ‡	1.00	1.19 (0.54-2.63)	0.63 (0.25-1.59)	0.60 (0.23-1.53)	0.78 (0.31-1.92)	0.32

*Nutrient values were energy-adjusted. Total magnesium intake was estimated from both dietary and supplemental sources.
†Model was adjusted for age and randomized treatment assignment.
‡Model was adjusted for variables denoted in †, and additionally for body mass index, family history of colorectal cancer in a first-degree relative, history of colon polyps, physical activity, smoking status, red meat intake, alcohol consumption, total energy intake, multivitamin use, menopausal status, and baseline postmenopausal HT use.
§Number of colon and rectal cases did not add up to the total colorectal cancer cases because the specific site was not specified for some cases.

is questionable whether the association observed in the other two cohorts truly reflects body magnesium stores or other unknown factors that are strongly associated with magnesium intake.

In this cohort, dietary magnesium accounted for >95% of total magnesium intake. Foods rich in magnesium include vegetables, fruits, grains, and dairy products. We have previously reported no associations of these foods rich in magnesium with colorectal cancer incidence (22, 23). It is therefore less surprising to observe the present null finding for magnesium intake. However, some limitations of the present study warrant more consideration. First, measurement error of nutrient intake due to random within-person error is inevitable because we only assessed intakes of nutrients once at baseline. Second, the possibility of residual confounding cannot be excluded although we have carefully controlled for a number of potential risk factors for colorectal cancer and did stratified analyses according to these confounding factors.

In conclusion, our data provide little support for an inverse association between total magnesium intake and colorectal cancer incidence. Because data relating magnesium intake to colorectal cancer are sparse, more studies are warranted to elucidate the true role of magnesium in colorectal cancer development.

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