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Magnesium Intake in Relation to Risk of Colorectal Cancer in Women

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Context Animal studies have suggested that dietary magnesium may play a role in the prevention of colorectal cancer, but data in humans are lacking.

Objective To evaluate the hypothesis that a high magnesium intake reduces the risk of colorectal cancer in women.

Design, Setting, and Participants The Swedish Mammography Cohort, a population-based prospective cohort of 61 433 women aged 40 to 75 years without previous diagnosis of cancer at baseline from 1987 to 1990.

Main Outcome Measure Incident invasive colorectal cancer.

Results During a mean of 14.8 years (911 042 person-years) of follow-up, 805 incident colorectal cancer cases were diagnosed. After adjustment for potential confounders, we observed an inverse association of magnesium intake with the risk of colorectal cancer (*P* for trend = .006). Compared with women in the lowest quintile of magnesium intake, the multivariate rate ratio (RR) was 0.59 (95% confidence interval [CI], 0.40-0.87) for those in the highest quintile. The inverse association was observed for both colon (RR, 0.66; 95% CI, 0.41-1.07) and rectal cancer (RR, 0.45; 95% CI, 0.22-0.89).

Conclusion This population-based prospective study suggests that a high magnesium intake may reduce the occurrence of colorectal cancer in women.

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Magnesium is required for a wide range of biological functions. Apart from being essential for the maintenance of genomic stability and for DNA repair, magnesium has a crucial role in modulating cell proliferation, cell cycle progression, and cell differentiation.[1] Magnesium supplementation has been demonstrated to reduce the incidence of experimentally induced colon cancer in animals,[2,3] which might be related to a decrease in colonic epithelial cell proliferation.[3-6] Magnesium has an important role in maintaining the antioxidative status of the cell[1]; animals deficient in magnesium display an increased susceptibility to oxidative stress.[1,7,8]

High circulating concentrations of C-peptide, a marker for insulin secretion, have been associated with increased risk of colorectal cancer in humans[9,10]; conceivably, dietary factors that improve insulin sensitivity and lower insulin concentrations may have an impact on colorectal cancer risk. Magnesium supplementation increased insulin sensitivity among healthy subjects[11] and among patients with type 2 diabetes.[12,13] Furthermore, recent epidemiologic studies reported an inverse association of magnesium intake with insulin concentrations.[14,15] Despite evidence that magnesium may be implicated in colorectal carcinogenesis, there is no epidemiologic study pertaining to the association between magnesium intake and risk of colorectal cancer. Therefore, we conducted a prospective analysis of magnesium intake in relation to incidence of colorectal cancer using data from the Swedish Mammography Cohort, a population-based prospective cohort of 61 433 women.

METHODS

Details of the Swedish Mammography Cohort have been described previously.[16] In brief, this population-based cohort was established between 1987 and 1990, when all women aged 40 to 75 years living in Uppsala and Västmanland counties, central Sweden, received a mailed questionnaire that elicited information about diet (along with data on weight, height, and educational level). In total, 66 651 women, representing 74% of the source population, returned a completed questionnaire. A new questionnaire, sent to all surviving participants in 1997, was expanded to include data on a family history of colorectal cancer, cigarette smoking, physical activity, and use of multivitamin supplements and aspirin. The study was approved by the ethics committee at the Karolinska Institutet in Stockholm and the Uppsala University Hospital.

Nutrient Intake Analysis

Nutrient intakes were computed by multiplying the consumption frequency of each food by the nutrient content of age-specific (<53, 53-65,

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≥66 years) servings, using composition values from the Swedish National Food Administration Database.[17] In a validation study in a subsample of 129 women randomly selected from the cohort (A. Wolk, unpublished data 1992), Pearson correlation coefficient between intake of magnesium reported in the baseline questionnaire and in four 1-week dietary records was 0.44, indicating reasonable validity of our questionnaire-based assessment of magnesium intake.

Exclusions

For this analysis, we excluded women with an erroneous national registration number, women with extreme energy intake estimates (ie, 3 SDs from the mean value for log-transformed energy), and women with previously diagnosed cancer (other than nonmelanoma skin cancer) at baseline. After exclusions, the study population comprised 61 433 eligible women who were followed up until a diagnosis of colorectal cancer, death, or June 30, 2004.

Statistical Methods

The women were categorized into quintiles according to magnesium intake. After determining that the data conformed to the proportional hazards assumptions, we used Cox proportional hazards modeling[18] with age in months as the underlying time variable to estimate rate ratios (RRs) with 95% confidence intervals (CIs). All multivariate models were also simultaneously adjusted for body mass index (BMI), educational level, and intakes of total energy, saturated fat, dietary fiber, calcium, zinc, beta carotene, folate, and vitamin B_6. Intakes of nutrients were adjusted for total energy intake with the residual method.[19] To calculate the *P* value for trend, participants were assigned the median value of their quintile of magnesium intake, and this variable was used as a continuous variable.[20] We used restricted cubic spline regression with 5 knots to flexibly model the association between magnesium intake and colorectal cancer risk.[21] Analyses were conducted using SAS software (version 8.2, SAS Institute Inc, Cary, NC). All *P* values were 2-tailed; $P<.05$ was considered statistically significant.

Table 1. Baseline Characteristics of Study Population According to Magnesium Intake in 61 433 Women in the Swedish Mammography Cohort*

Characteristic	Quintiles of Energy-Adjusted Magnesium Intake, Range (Median), mg/d				
	<209 (198)	209-224 (218)	225-237 (232)	238-254 (246)	≥255 (268)
No. of participants	12 170	12 757	11 655	12 438	12 413
Age at baseline, mean (SD), y	53.4 (9.9)	53.3 (9.8)	53.4 (9.7)	53.9 (9.7)	54.6 (9.6)
BMI, mean (SD)†	24.7 (4.0)	24.6 (3.8)	24.7 (3.8)	24.7 (3.8)	24.9 (3.9)
Postsecondary education, %‡	10.9	12.1	13.0	13.3	14.0
Dietary intake, mean (SD)§					
Total energy, kcal/d	1385 (403)	1372 (373)	1344 (359)	1306 (361)	1240 (362)
Saturated fat, g/d	20.6 (4.5)	19.6 (3.7)	18.0 (3.4)	16.8 (3.3)	14.7 (3.3)
Dietary fiber, g/d	12.2 (2.9)	14.5 (2.9)	15.9 (3.0)	17.4 (3.3)	19.9 (4.1)
Calcium, mg/d	621 (178)	671 (173)	699 (175)	725 (188)	778 (224)
Zinc, mg/d	6.8 (1.0)	7.3 (0.9)	7.5 (0.9)	7.7 (0.9)	8.0 (1.0)
Beta carotene, mg/d	1.8 (1.2)	2.2 (1.3)	2.5 (1.5)	2.9 (1.8)	3.9 (2.9)
Folate, μg/d	147 (27)	168 (26)	180 (28)	194 (31)	225 (53)
Vitamin B_6, mg/d	1.2 (0.2)	1.3 (0.2)	1.4 (0.2)	1.5 (0.2)	1.6 (0.3)

*Age-standardized to the age distribution of the entire study cohort from 1987 to 1990.
†Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.
‡Percentage of women with 12 or more years of education.
§All nutrients were energy-adjusted with use of the residual method.[19]

RESULTS

The age-standardized baseline characteristics of the study population by quintiles of magnesium intake are shown in TABLE 1. Compared with women with a low intake of magnesium, those with higher intakes generally had lower intakes of energy and saturated fat and higher intakes of dietary fiber, calcium, zinc, beta carotene, folate, and vitamin B_6. Women with greater magnesium intake also were more likely to have a postsecondary education.

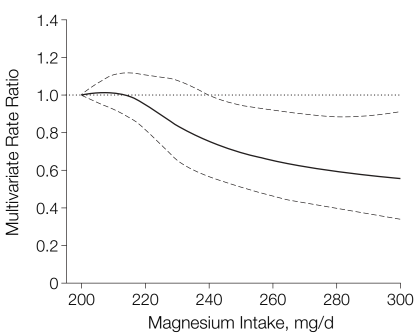
Over an average follow-up of 14.8 years (911 042 person-years), 805 women were diagnosed with colorectal cancer (547 colon cancer, 252 rectal cancer, and 6 cases with both colon and rectal cancer). We observed a statistically significant inverse association between magnesium intake and risk of colorectal cancer in both the age- and multivariate-adjusted models (TABLE 2). Compared with women in the lowest quintile of magnesium intake, the multivariate RR of colorectal cancer for those in the highest quintile was 0.59 (95% CI, 0.40-0.87; *P* for trend = .006). Further control for consumption of red meat, fruits, vegetables, and whole grain foods yielded virtually the same results (RR, 0.61; 95% CI, 0.41-0.91). In addition, the inverse association with magnesium intake persisted when we added 1 at a time to a multivariate model intake of vitamins A, C, D, and E, and (in place of total dietary fiber) cereal fiber, vegetable fiber, and fruit fiber (data not shown). The RR was only slightly attenuated when all these nutrients were included simultaneously in a multivariate model (RR, 0.67; 95% CI, 0.45-1.00). Using data from the 1997 questionnaire, the results remained essentially unchanged after adjustment for a family history of colorectal cancer, cigarette smoking, physical activity, and use of multivitamin supplements and aspirin (RR, 0.60; 95% CI, 0.40-0.88). Excluding cases of colorectal cancer that occurred within the first 3 years of follow-up did not appreciably alter the results (multivariate RR comparing extreme quintiles, 0.62; 95% CI, 0.41-0.93). Intake of magnesium was inversely associated with both colon and

Table 2. Rate Ratio of Colorectal Cancer According to Magnesium Intake

	Quintiles of Energy-Adjusted Magnesium Intake, mg/d					
	<209	209-224	225-237	238-254	≥255	*P* Value for Trend
Colorectal cancer						
No. of cases	180	171	147	154	153	
Age-adjusted RR (95% CI)	1.00	0.89 (0.72-1.10)	0.82 (0.66-1.02)	0.77 (0.62-0.95)	0.74 (0.60-0.92)	.003
Multivariate RR (95% CI)*	1.00	0.86 (0.68-1.09)	0.77 (0.58-1.02)	0.68 (0.49-0.94)	0.59 (0.40-0.87)	.006
Colon cancer†						
No. of cases	118	121	103	106	99	
Age-adjusted RR (95% CI)	1.00	0.96 (0.75-1.25)	0.88 (0.67-1.14)	0.81 (0.62-1.05)	0.74 (0.56-0.96)	.01
Multivariate RR (95% CI)*	1.00	1.00 (0.75-1.34)	0.92 (0.65-1.30)	0.82 (0.55-1.21)	0.66 (0.41-1.07)	.08
Rectal cancer‡						
No. of cases	58	49	44	48	53	
Age-adjusted RR (95% CI)	1.00	0.78 (0.53-1.15)	0.75 (0.50-1.11)	0.74 (0.50-1.09)	0.78 (0.54-1.13)	.20
Multivariate RR (95% CI)*	1.00	0.64 (0.41-0.98)	0.54 (0.33-0.90)	0.48 (0.27-0.84)	0.45 (0.22-0.89)	.02

Abbreviations: CI, confidence interval; RR, rate ratio.
*Adjusted for age (in months), body mass index (quartiles), educational level (less than high school, high school, university), total energy intake (quartiles), and energy-adjusted intakes of saturated fat, dietary fiber, calcium, zinc, beta carotene, folate, and vitamin B_6 (all in quartiles).
†Colon cancers were defined as those from the cecum through the sigmoid colon (including 249 proximal colon, 170 distal colon, and 128 cancers at an unspecified subsite in the colon).
‡Rectal cancers included tumors in the rectum and rectosigmoid junction. Cases diagnosed with both colon and rectal cancer (n = 6) were not included in subsite-specific analyses.

Figure. Colorectal Cancer According to Magnesium Intake



Multivariate rate ratios calculated by restricted cubic spline Cox proportional hazards model. Rate ratios are adjusted for age (in months), body mass index (quartiles), educational level (less than high school, high school, university), total energy intake (quartiles), and energy-adjusted intakes of saturated fat, dietary fiber, calcium, zinc, beta carotene, folate, and vitamin B_6 (all in quartiles). Solid curve represents point estimates and dashed curves represent 95% confidence intervals.

rectal cancer (Table 2); the inverse association was similar for proximal colon (RR comparing extreme quintiles, 0.56; 95% CI, 0.27-1.16) and distal colon cancer (RR, 0.63; 95% CI, 0.27-1.47).

Because the inverse association of magnesium intake with colorectal cancer risk appeared to be linear (FIGURE), we analyzed magnesium intake as a continuous variable. The multivariate RR of colorectal cancer for a 50-mg/d increment of magnesium—approximately equivalent to the magnesium content in 1 small serving of spinach per day, 1 large banana per day, 1 serving of cooked oatmeal per day, 2 slices of whole grain bread per day, or a half serving of beans per day—was 0.78 (95% CI, 0.62-0.99).

COMMENT

This large population-based prospective cohort study is, to the best of our knowledge, the first to examine and observe a significant inverse dose-response relationship between magnesium intake and risk of colorectal cancer.

Major strengths of our study include its large size, population-based and prospective design, the large number of colorectal cancer cases, and the completeness of case ascertainment through the Swedish Cancer Registry System.[22] These features of the study increase the generalizability of our results and eliminate potential recall and selection biases. Our study also has several potential limitations. Because magnesium intake was assessed through a self-administered food-frequency questionnaire, and our analysis was based on a single baseline measurement of dietary intake, some misclassification of magnesium intake is inevitable, which would potentially attenuate any true relationship. Although we adjusted our estimates for a wide range of potential confounders, we cannot rule out the possibility that our findings may be biased by unmeasured confounders or by residual confounding. However, multivariate analyses yielded results similar to those from age-adjusted analyses, suggesting that residual confounding is unlikely to have affected our results materially.

In conclusion, this population-based cohort study of women suggests that a high magnesium intake may reduce the risk of colorectal cancer. While our findings require confirmation by other large well-designed studies, they support potential benefits of increasing consumption of major foods contributing to magnesium intake, including fruits and vegetables, whole grain foods, and beans, in reducing colorectal cancer incidence. However, the efficiency and safety of magnesium supplementation for the prevention of colorectal cancer needs to be specifically addressed in a randomized trial.

Author Contributions: Ms Larsson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Larsson, Bergkvist, Wolk.
Acquisition of data: Wolk.
Analysis and interpretation of data: Larsson, Wolk.
Drafting of the manuscript: Larsson.
Critical revision of the manuscript for important intellectual content: Larsson, Bergkvist, Wolk.
Statistical analysis: Larsson.

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REFERENCES

1. Hartwig A. Role of magnesium in genomic stability. *Mutat Res*. 2001;475:113-121.
2. Tanaka T, Shinoda T, Yoshimi N, Niwa K, Iwata H, Mori H. Inhibitory effect of magnesium hydroxide on methylazoxymethanol acetate-induced large bowel carcinogenesis in male F344 rats. *Carcinogenesis*. 1989;10:613-616.
3. Mori H, Morishita Y, Shinoda T, Tanaka T. Preventive effect of magnesium hydroxide on carcinogen-induced large bowel carcinogenesis in rats. *Basic Life Sci*. 1993;61:111-118.
4. Mori H, Morishita Y, Mori Y, Yoshimi N, Sugie S, Tanaka T. Effect of magnesium hydroxide on methylazoxymethanol acetate-induced epithelial proliferation in the large bowels of rats. *Cancer Lett*. 1992;62:43-48.
5. Wang A, Yoshimi N, Tanaka T, Mori H. Inhibitory effects of magnesium hydroxide on c-myc expression and cell proliferation induced by methylazoxymethanol acetate in rat colon. *Cancer Lett*. 1993;75:73-78.
6. Wang A, Yoshimi N, Tanaka T, Mori H. The inhibitory effect of magnesium hydroxide on the bile acid-induced cell proliferation of colon epithelium in rats with comparison to the action of calcium lactate. *Carcinogenesis*. 1994;15:2661-2663.
7. Gueux E, Azais-Braesco V, Bussiere L, Grolier P, Mazur A, Rayssiguier Y. Effect of magnesium deficiency on triacylglycerol-rich lipoprotein and tissue susceptibility to peroxidation in relation to vitamin E content. *Br J Nutr*. 1995;74:849-856.
8. Hans CP, Chaudhary DP, Bansal DD. Effect of magnesium supplementation on oxidative stress in alloxanic diabetic rats. *Magnes Res*. 2003;16:13-19.
9. Kaaks R, Toniolo P, Akhmedkhanov A, et al. Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. *J Natl Cancer Inst*. 2000;92:1592-1600.
10. Ma J, Giovannucci E, Pollak M, et al. A prospective study of plasma C-peptide and colorectal cancer risk in men. *J Natl Cancer Inst*. 2004;96:546-553.
11. Paolisso G, Sgambato S, Gambardella A, et al. Daily magnesium supplements improve glucose handling in elderly subjects. *Am J Clin Nutr*. 1992;55:1161-1167.
12. Paolisso G, Sgambato S, Pizza G, Passariello N, Varricchio M, D'Onofrio F. Improved insulin response and action by chronic magnesium administration in aged NIDDM subjects. *Diabetes Care*. 1989;12:265-269.
13. Sjogren A, Floren CH, Nilsson A. Oral administration of magnesium hydroxide to subjects with insulin-dependent diabetes mellitus: effects on magnesium and potassium levels and on insulin requirements. *Magnesium*. 1988;7:117-122.
14. Fung TT, Manson JE, Solomon CG, Liu S, Willett WC, Hu FB. The association between magnesium intake and fasting insulin concentration in healthy middle-aged women. *J Am Coll Nutr*. 2003;22:533-538.
15. Song Y, Manson JE, Buring JE, Liu S. Dietary magnesium intake in relation to plasma insulin levels and risk of type 2 diabetes in women. *Diabetes Care*. 2004;27:59-65.
16. Wolk A, Bergstrom R, Hunter D, et al. A prospective study of association of monounsaturated fat and other types of fat with risk of breast cancer. *Arch Intern Med*. 1998;158:41-45.
17. Bergström L, Kylberg E, Hagman U, Erikson H, Bruce Å. The food composition database KOST: the National Food Administration's information system for nutritive values of food. *Vår Föda*. 1991;43:439-447.
18. Cox DR, Oakes D. *Analysis of Survival Data*. London, England: Chapman & Hall; 1984.
19. Willett WC. *Nutritional Epidemiology*. 2nd ed. New York, NY: Oxford University Press; 1998.
20. Rothman KJ. *Modern Epidemiology*. 2nd ed. Philadelphia, Pa: Lippincott-Raven; 1998.
21. Durrleman S, Simon R. Flexible regression models with cubic splines. *Stat Med*. 1989;8:551-561.
22. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register: non-notified cancer cases recorded on death certificates in 1978. *Acta Radiol Oncol*. 1984;23:305-313.

When I am working on a problem I never think about beauty. I only think about how to solve the problem. But when I have finished, if the solution is not beautiful, I know it is wrong.
—R. Buckminster Fuller (1895-1983)