Magnesium Intake in Relation to Risk of Colorectal Cancer in Women

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In Reply:
Magnesium Intake in Relation to Risk of Colorectal Cancer in Women

Susanna C. Larsson, MSc
Leif Bergkvist, MD, PhD
Alicja Wolk, DMSc

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. magnesium supplementation has been demonstrated to reduce the incidence of experimentally induced colon cancer in animals, which might be related to a decrease in colonic epithelial cell proliferation. Magnesium has an important role in maintaining the antioxidative status of the cell; animals deficient in magnesium display an increased susceptibility to oxidative stress.

High circulating concentrations of C-peptide, a marker for insulin secretion, have been associated with increased risk of colorectal cancer in humans; 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 and among patients with type 2 diabetes. Furthermore, recent epidemiologic studies reported an inverse association of magnesium intake with insulin concentrations.

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. 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, 66,631 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 publications.
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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 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 B₆. Intakes of nutrients were adjusted for total energy intake with the residual method. 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. We used restricted cubic spline regression with 5 knots to flexibly model the association between magnesium intake and colorectal cancer risk. 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.

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 B₆. 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
MAGNESIUM INTAKE AND COLORECTAL CANCER

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

<table>
<thead>
<tr>
<th>Quintiles of Energy-Adjusted Magnesium Intake, mg/d</th>
<th>No. of cases</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;209</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>209-224</td>
<td>171</td>
<td></td>
</tr>
<tr>
<td>225-237</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td>238-254</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>≥255</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.00</td>
<td>0.89 (0.72-1.10)</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)*</td>
<td>1.00</td>
<td>0.86 (0.68-1.09)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, rate ratio.
*Adjusted for age (in months), body mass index (quartiles), education (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 B6 (all in quartiles).
†Colorectal 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 rectum). 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

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 systematically 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.
Obtained funding: Bergkvist, Wolk.
Administrative, technical, or material support: Wolk.
Study supervision: Bergkvist, Wolk.

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REFERENCES


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)