Magnesium Intake and Reduced Risk of Colon Cancer in a Prospective Study of Women

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A recent prospective study among Swedish women suggested an inverse association of dietary magnesium intake with incidence of colorectal cancer. The authors assessed this association in a cohort of 35,196 Iowa women initially free of cancer and aged 55–69 years in 1986. Intakes of magnesium and other nutrients were assessed by food frequency questionnaire at baseline. Over 17 years of follow-up through 2002, 1,112 women developed colorectal cancer. After adjustment for age, energy, other nutrients, and risk factors for colorectal cancer, the hazard ratios of colorectal cancer across quintiles of magnesium intake were 1.00, 0.96, 0.83, 0.87, and 0.80 (95% confidence interval: 0.62, 1.03; \( p_{\text{trend}} = 0.06 \)). The association was largely absent for rectal cancer but, for colon cancer, the hazard ratios were 1.00, 1.00, 0.88, 0.85, and 0.77 (95% confidence interval: 0.58, 1.03; \( p_{\text{trend}} = 0.04 \)). These findings offer further evidence that a diet high in magnesium may reduce the occurrence of colon cancer among women. If replicated by other observational studies, a clinical trial would be needed to determine whether it is magnesium, specifically, and not other aspects of the contributing foods, that may offer benefit.

Materials and Methods

The Iowa Women’s Health Study cohort involved 41,836 women aged 55–69 years recruited via a baseline questionnaire mailed in 1986. A previous report explained how self-reported baseline risk factors were assessed and defined (2). We assessed baseline dietary intake by use of a 127-item food frequency questionnaire, created by Willett (3) and validated in this cohort by Munger et al. (4). Women who left greater than 30 food frequency items blank or had extreme energy intakes (<600 kcal/day or \( \geq 5,000 \) kcal/day) were excluded. Intakes of magnesium and other nutrients from foods or supplements were assigned using the Harvard database. Nutrients were adjusted for energy intake by the residual method (5).

We identified cancer incidence and most deaths through 2002 by annual linkage of cohort identifiers to Iowa cancer registries, and deaths were ascertained through linkage to the National Death Index. Mortality was considered to be due to colorectal cancer if the International Classification of Diseases code was 153.0–153.9. Cancer incidence was assessed by using International Classification of Diseases codes 153.0–153.9, 154.0–154.9, 155.0–155.9, and 156.0–156.9. After exclusion of deaths from other causes, the number of years of follow-up was 266,236 person-years, with 1,112 cancer events. The number of person-years at risk for each quintile of magnesium is presented in Table 1. The hazard ratios of colorectal cancer across quintiles of magnesium intake were 1.00, 0.96, 0.83, 0.87, and 0.80 (95% confidence interval: 0.62, 1.03; \( p_{\text{trend}} = 0.06 \)). The association was largely absent for rectal cancer but, for colon cancer, the hazard ratios were 1.00, 1.00, 0.88, 0.85, and 0.77 (95% confidence interval: 0.58, 1.03; \( p_{\text{trend}} = 0.04 \)). These findings offer further evidence that a diet high in magnesium may reduce the occurrence of colon cancer among women. If replicated by other observational studies, a clinical trial would be needed to determine whether it is magnesium, specifically, and not other aspects of the contributing foods, that may offer benefit.

Larsson et al. (1) recently reported a moderately strong inverse association between magnesium intake and incidence of colorectal cancer in a cohort of Swedish women aged 40–75 years, with a rate ratio of approximately 0.6 for the highest versus lowest quintiles of magnesium intake. The inverse association was independent of other colorectal cancer risk factors and was observed for both colon and rectal cancer. Larsson et al. (1) cited evidence that magnesium may prevent colon cancer by reducing oxidative stress, by improving insulin sensitivity, or by other means of decreasing colonic epithelial cell proliferation. As there appear to be no other prospective studies, we sought to corroborate the association of magnesium intake with colorectal cancer in the Iowa Women’s Health Study, including possible heterogeneity of association across other characteristics.

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incidence and death records and by questionnaires mailed to the cohort in 1987, 1989, 1992, and 1997. To find additional deaths, we sent identifiers of nonrespondents to the follow-up questionnaires to the National Death Index. Colorectal cancer comprised International Classification of Diseases for Oncology, Second Edition, codes C18 (colon) and C19 (rectum).

A total of 35,196 women were initially free of cancer and had usable food frequency questionnaire data. For comparison with the results of Larsson et al. (1), our data on energy-adjusted magnesium intake were categorized into quintiles. Baseline characteristics were compared across magnesium quintiles by use of analysis of covariance. We used proportional hazards regression to estimate hazard ratios, adjusted for age and other risk factors for colorectal cancer in this (6–10) or the Swedish (1) cohort (i.e., age, energy, saturated fat, calcium, folate, vitamin E, dietary fiber, zinc, beta-carotene, vitamin B₆, diabetes, body mass index, physical activity, cigarettes, and estrogen replacement). We tested the trend in hazard ratios across quintiles by modeling an ordinal variable indicating each quintile.

### RESULTS

The mean magnesium intake was 302 (standard deviation: 109) mg/day, of which 289 mg/day were from food and 13 mg/day were from supplements and multivitamins, taken altogether by 15 percent of women. Most baseline risk factors for colorectal cancer were inversely associated with magnesium intake (table 1).

During follow-up over 17 years, 1,112 women developed colorectal cancer. There was an inverse association between magnesium intake and colorectal cancer incidence (table 2). The association was observed for colon cancer but not for rectal cancer. The multivariately adjusted hazard ratio of colon cancer for the highest versus lowest quintile of magnesium intake was approximately 0.8. In supplemental analyses, adjustment for frequency of aspirin use (assessed in 1992) or for baseline iron intake had no impact on the findings, nor was there an iron-by-magnesium interaction.

The inverse association between magnesium intake and colon cancer showed little heterogeneity by several of the baseline subgroups examined. By use of a median split for high versus low magnesium intake, the multivariate-adjusted hazard ratio of colon cancer was 0.88 in nonusers of hormonal replacement therapy versus 1.14 in users, and it was 0.70 in diabetic women versus 0.92 in nondiabetic women (both interactions not significant; \( p > 0.05 \)). The hazard ratio was even more homogeneous across strata of obesity, smoking, and physical activity (data not shown).

In the multivariate model (table 2), calcium independently was associated with colorectal and colon cancer...
incidence. The hazard ratios per 500-mg/day increment of calcium were 0.91 (95 percent confidence interval: 0.85, 0.98) for colorectal cancer and 0.91 (95 percent confidence interval: 0.84, 0.99) for colon cancer. Energy intake was inversely associated with colorectal cancer incidence. The other dietary covariates were actually not associated (p > 0.10) with colorectal cancer at this point in follow-up. Other significant colorectal cancer risk factors were age, greater body mass index, diabetes, physical inactivity, and nonuse of estrogen.

**DISCUSSION**

In this cohort of Iowa women, we observed an inverse association of magnesium intake with colon cancer but not rectal cancer. The recent Swedish study (11) reported a somewhat stronger inverse association than we found for colon cancer but also an inverse association for rectal cancer. We are uncertain why the two studies differ with respect to magnesium and rectal cancer.

Our study cannot elucidate why greater magnesium intake may offer potential benefit against colon cancer; however, reductions of insulin resistance, oxidative stress, and cell proliferation (1) are plausible mechanisms. Intake of calcium also has a salutary effect against colon cancer (6–8, 13). With longer follow-up than in previous reports, calcium remained inversely associated with colorectal and colon cancer occurrence but, as expected, several other dietary associations had weakened with 17-year follow-up.

Our prospective, population-based study was large and was able to consider many potentially confounding variables. Study limitations include an ethnic homogeneity in Iowa that restricts generalizability; the inherent measurement error of dietary assessment performed only once, though this error would be expected to be nondifferential; and a general difficulty of pinpointing individual nutrients, such as low magnesium intake, as causative risk factors in observational studies. A theoretical limitation is “detection bias,” whereby women with lower magnesium intake might have had greater screening and more colorectal cancers detected. However, this seems unlikely, because healthy lifestyle habits that might correlate with greater screening were more prevalent in the higher, rather than the lower, quintiles of magnesium intake.

These findings offer further evidence that a diet high in magnesium may reduce the occurrence of colon cancer among women. It is unclear whether this indicates a causal role for magnesium in the suppression of colon cancer, or whether it is simply that other aspects of high-magnesium foods are important. If the association is further replicated by observational studies, a clinical trial would be needed to determine whether it is magnesium, specifically, that may offer benefit.

**TABLE 2. Hazard ratio of colorectal cancer according to magnesium intake, Iowa Women’s Health Study,† 1986–2002**

<table>
<thead>
<tr>
<th>Quintiles of energy-adjusted magnesium intake (mg/day)</th>
<th>&lt;245</th>
<th>245–276</th>
<th>277–306</th>
<th>307–351</th>
<th>&gt;351</th>
<th>Pr<strong>trend</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colorectal cancer (n = 1,112)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age adjusted</td>
<td>1.00</td>
<td>0.99</td>
<td>0.83, 1.17</td>
<td>0.84</td>
<td>0.70, 1.01</td>
<td>0.84</td>
</tr>
<tr>
<td>Multivariate†</td>
<td>1.00</td>
<td>0.96</td>
<td>0.80, 1.16</td>
<td>0.83</td>
<td>0.68, 1.02</td>
<td>0.87</td>
</tr>
<tr>
<td><strong>Colon cancer (n = 990)</strong>†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age adjusted</td>
<td>1.00</td>
<td>1.01</td>
<td>0.83, 1.23</td>
<td>0.88</td>
<td>0.72, 1.08</td>
<td>0.84</td>
</tr>
<tr>
<td>Multivariate†</td>
<td>1.00</td>
<td>1.00</td>
<td>0.81, 1.22</td>
<td>0.88</td>
<td>0.71, 1.10</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Rectal cancer (n = 236)</strong>†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age adjusted</td>
<td>1.00</td>
<td>0.90</td>
<td>0.61, 1.32</td>
<td>0.66</td>
<td>0.44, 1.01</td>
<td>0.88</td>
</tr>
<tr>
<td>Multivariate†</td>
<td>1.00</td>
<td>0.87</td>
<td>0.59, 1.30</td>
<td>0.65</td>
<td>0.42, 1.02</td>
<td>0.94</td>
</tr>
</tbody>
</table>

* In the Iowa Women’s Health Study, 35,196 women were initially free of cancer and had usable food frequency questionnaire data.
† Model 2 (n = 33,837 due to missing covariates) adjusted for age; intake of energy; energy-adjusted saturated fat, calcium, folate, vitamin E, zinc, beta-carotene, vitamin B6, and dietary fiber; diabetes (yes, no); body mass index (continuous); physical activity (low, medium, high); pack-years of cigarettes (0, 1–19, 20–39, ≥40); and estrogen replacement (current, former, never).
‡ Includes 14 women with both colon cancer and rectal cancer.

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REFERENCES